Healthcare Improvement Scotland | SIGN Evidence-based clinical guidelines

Management of chronic pain

A national clinical guideline

Draft for consultation (Waves 1 and 2) February 2025

NHS SCOTLAND

Key to evidence statements and recommendations

Levels of evidence

1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Sufficient / insufficient - Network meta-analyses are given a binary rating according to relevance and credibility

Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

R For '**strong**' recommendations on interventions that **'should'** be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that **'should not'** be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

R For '**conditiona**l' recommendations on interventions that should be '**considered'**, the guideline development group is confident that the intervention will do more good than harm for **most** patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Good-practice points

✓ Recommended best practice based on the clinical experience of the guideline development group.

Contents

1 Introduction

1.1 The need for a guideline

Chronic pain is pain that persists for more than three months, or beyond normal injury healing time.[1] It is a major clinical and public health challenge: prevalence figures vary, with estimates between 35.0 to 51.3% in the UK, increasing with age (18-25 years old: 14.3%; over 7 years old: 62%).[2] The prevalence of moderate to severely disabling chronic pain is up to 14.3%. It has a considerable impact on quality of life, resulting in significant suffering and disability.[3-5] Globally, back pain remains the leading cause of years lived with disability.[6] While in many cases it is accepted that a cure is unlikely, the impact on quality of life, mood and function can be significantly reduced by appropriate management. Chronic pain not only has an impact on affected individuals and their families, it also has substantial economic costs, although accurate up-to-date figures for these are hard to obtain. For example, back pain alone was estimated to cost £12 billion per annum in the UK in 1998, and arthritis-associated pain costs around 2.5% of the gross national product of Western nations.[7,8] A more recent Norwegian study of healthcare and work absence costs estimated that 4% of gross domestic product (GDP) was spent on chronic pain.[9]

While a proportion of patients will require access to specialist secondary and tertiary care pain services, the majority of patients will be managed in the community or primary care. It is vital that general practitioners (GPs) and other healthcare professionals have the best possible resource and support to manage their patients properly and have facilities for accessing appropriate specialist services when required. Within Scotland there is evidence of wide variation in clinical practice service and resource provision, with a general lack of knowledge about chronic pain and the management options that are available.[10,11]

A wide range of both pharmacological and non-pharmacological management strategies are available for chronic pain. The challenge is to understand the extensive published evidence for different treatments and to determine when and where to use them for the best long-term outcomes. It is hoped that this evidence-based guideline will provide the information needed to improve clinical outcomes and quality of life for people with chronic pain.

1.1.1 Lived-experience perspective

People with lived experience may have different perspectives on healthcare processes and outcomes from those of healthcare professionals. The involvement of people with lived experience in guideline development is therefore important to ensure that guidelines reflect their needs and concerns and address issues that matter to them.

Common concerns raised by groups and organisations and through research[12] include:

- raising awareness and improving pathways for supported self management in all people affected by chronic pain and ensuring it can be delivered on an ongoing basis to adequately support individuals in the longer term.
- more public information about what chronic pain is, its impact on people in Scotland and how to access support.
- information about the different types of treatment available for chronic pain and when they are used.
- information about what services and health and care teams are available locally and how they might help individuals to manage their pain closer to home.
- access to support to help individuals manage the impact of their pain on their mental health and wellbeing.

Healthcare Improvement Scotland gathered information from people in Scotland living with chronic pain to support the Scottish Government Framework for Pain Management Service Delivery.[13] The work involved gathering lived experience from individuals living with chronic pain by asking questions about the care and support they had experienced through health and social care services and local support groups. The report summarises feedback from 92 people with chronic pain and includes recommendations for improved service delivery in the following areas:

- staff understanding and attitudes
- access to support services
- different types of support
- self management
- feedback from people with lived experience.

SIGN will publish a plain language version of this guideline alongside the full version in order to:

- help people understand the latest evidence around diagnosis, treatment, and self-care
- empower people to actively participate in decisions about managing their condition in discussions with health and social care professionals
- highlight areas of uncertainty for people, making them aware of where more information or research is needed.

1.2 Remit of the guideline

1.2.1 Overall objectives

This guideline provides recommendations based on current evidence for best practice in the management of adults with chronic non-malignant pain in non-specialist settings.

It does not cover:

- interventions which can only be delivered in secondary/tertiary care.
- treatment of patients with migraine or headache (*see SIGN 155, Pharmacological management of migraine*).[14]
- pain caused by cancer.
- children. While chronic pain occurs in children, some of their treatment options are different to those of adults, and evidence on the paediatric population has not been included in this remit (*see the Scottish Government guideline Management of chronic pain in children and young people*[15] *and World Health Organization (WHO) guideline on the management of chronic pain in children.*[16]*)*
- underlying conditions. Chronic pain is caused by many underlying conditions. The treatment of these conditions is not the focus of this guideline so the search strategies were restricted to the treatment of chronic pain, not specific conditions.

In order to ensure that the recommendations are available as soon as possible, this SIGN guideline has been developed sequentially, with each component containing review of several research questions (see Annex 1). The order in which this is being done does not reflect the relative important of the questions, nor strength of available evidence. This document contains information on:

- opioids
- naloxone
- medicinal cannabis
- antidepressants
- pain management programmes
- psychological interventions
- self-help interventions, and
- occupation-based interventions.

SIGN will circulate further documents for consultation containing information relating to the remaining topics when available.

1.2.2 Comorbidities to consider when managing patients with chronic pain

The prevalence of chronic pain increases with age with one systematic review reporting prevalence of 14.3% in those aged 18–25 years rising to 62% in those over 75 years.[2] Older adults are at increased risk of multimorbidity, including cardiovascular disease, dementia and renal disease with consequential increased risk of experiencing pain and incapacity. The existence of multimorbidity in the ageing population can also impact on overall medication safety.[17]

Common comorbidities and coexisting health issues which have been considered when reviewing the evidence for this guideline are:

- mood disorders (including depression and anxiety)
- cardiovascular disease and stroke
- diabetes
- surgical and medical interventions
- obesity.[18]

1.2.3 Target users of the guideline

This guideline will be of particular interest to all healthcare professionals involved in the assessment and management of people with chronic pain, including general practitioners, pharmacists, anaesthetists, psychologists, psychiatrists, physiotherapists, rheumatologists, occupational therapists, and nurses. Importantly, this guideline is also for people with chronic pain, carers and voluntary organisations with an interest in chronic pain as a resource containing recommendations and which summarises the supporting evidence. This aims to support a more effective partnership between healthcare professionals and people living with chronic pain, to improve management.

1.3 Definitions and classification of chronic pain

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[19] In this guideline chronic pain is defined as pain that has been present for more than 3 months.

The Scottish Government recognised chronic pain as a long-term condition in its own right in 2009. However, it is only in the most recent International Classification of Diseases (ICD-11) that there has been a comprehensive and systematic classification developed for chronic pain.[20,21] The ICD is the main tool used in many countries for coding diagnoses and interventions but the lack of effective coding for chronic pain to date has led to major deficiencies in epidemiological understanding of chronic pain and its impact. The new ICD-11 chronic pain coding is a significant advance, which will help to advance the recognition of chronic pain in primary care as an important condition, supporting service planning, education and research for chronic pain.[22]

This guideline covers management that can be delivered in the non-specialist setting, defined as any setting where the training and infrastructure is not specifically designed for treating chronic pain. This might include management in the community, primary care or secondary care.

1.4 Reporting in pain trials

Difficulties in reporting make the interpretation of the evidence base

challenging. Chronic pain is a complex phenomenon with consequent challenges for its assessment and management both in clinical trials and routine clinical practice. This is further complicated by the fact that even in the same condition the underlying pain mechanisms may differ significantly between individuals. While changes in peripheral pain processing might predominate in one patient, central changes may be much more important in the next patient with implications for the most effective treatment approaches in each case.[23-25]

These limitations have been recognised internationally, leading to the development of the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT, www.immpact.org) in 2002. In clinical trials, unless there is careful assessment of the chronic pain syndrome in each patient, potentially useful treatments may be discarded as being ineffective when the average response is considered. Even good quality, adequately powered double blind randomised controlled trials may not provide the best approach for developing a strong evidence base for pain management.[26-28] Innovative approaches to the methodology of clinical pain trials are needed, taking into consideration a number of factors, including entry criteria (eg, baseline pain scores),[29] and individual variation in treatment response.[30] Pragmatic clinical trials which bridge the translational gap between tightly controlled explanatory clinical trials and real world clinical effectiveness may be one approach to be considered.[26] Furthermore, ensuring robust involvement of people with chronic pain throughout the research cycle has been recognised as important:[31] to ensure relevance of study questions, appropriate study design and meaningful outcome measures, including consideration of composite measures (that reflect not just pain intensity but its wider impact).[32]

A number of factors need to be considered in order to optimise the design of trials studying chronic pain. These include patient selection (pain diagnosis, duration, intensity) and sample size, different phases within the trial (eg enriched enrolment) and duration of study, treatment groups (including active versus inactive placebo comparator), dosing strategies (fixed versus flexible) and type of trial (eg parallel, crossover).[26,28,33]

To allow comparison between studies a standardised approach to outcome measures, is recommended by IMMPACT.[26] Four key domains were recommended to adequately assess outcomes:

1. *Pain intensity*. A numerical rating scale 0-10 is recommended as the most practical and sensitive.
2. *Physical functioning*. Assessment with validated self-report questionnaires such as the Multidimensional Pain Inventory or Brief Pain Inventory interference scales is recommended.
3. *Emotional functioning*. The Beck Depression Inventory and the Profile of Mood States are recommended.
4. *Patient rating of overall improvement*. The Patient Global Impression of Change scale can be used.

Side effects and detailed information about patient recruitment and

progress through the trial should also be recorded.[34,35]

While much of the literature published to date does provide a sound evidence base for this guideline, it is hoped that future studies will follow the IMMPACT recommendations.

In addition to the limitations of assessment and trial design, concerns have been raised about how analysis methods may either obscure clinically important positive outcomes, or overestimate treatment effects. If the average response is considered, a treatment may appear ineffective, whereas it could have the potential to be effective in a particular subgroup of the patients being studied. It may, therefore, be useful to analyse responders to a particular treatment separately from non-responders.[28]

Another important factor is how patients who drop out before completing the study are dealt with in the analysis. Using the last-observation-carried-forward (LOCF) for patients who drop out is based on the assumption that in a randomised controlled trial (RCT) drop-outs will occur randomly between the treatment groups. The active treatment may be an effective analgesic but if it has an unpleasant side effect profile then drop-outs are likely to be higher in a non-random manner in this treatment group. Pain scores prior to drop-out may therefore demonstrate efficacy, but in clinical practice this treatment is unlikely to be tolerated. The majority of RCTs use the imputation method of LOCF, and may therefore potentially overestimate the treatment effect.[36]

While there are a number of good quality systematic reviews and meta-analyses that provide an evidence base for the management of patients with chronic pain, there are some limitations with the published primary literature. This has been taken into consideration by the guideline development group when appraising the evidence and, where there are areas of potential doubt, recommendations have been downgraded accordingly. Research recommendations have been made where clear gaps and limitations in the evidence were identified (*see section 11.2*).

1.4.1 What is a clinically important difference?

While proof of the statistical significance of trial results may be established by inferential statics, such as a p value, a more directly applicable question for healthcare professionals is whether or not results are also clinically important. The concept of the minimum clinically-important difference (MCID) was introduced to determine and communicate whether there was clinical relevance associated with the observed differences between treatments in a clinical trial. It has been defined as “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management.”[37] There is no agreement on a single MCID for people living with chronic pain as it is recognised to vary between different patient populations and the various health outcome measures used in clinical trials. Variability may also be seen among studies examining the same patient population as a result of differences in study design, study location, and treatment administered.

A systematic review, including 66 studies of treatments for chronic pain found a median absolute MCID of 23 mm on a 0–100 mm scale (interquartile range (IQR) 12–39), with very high heterogeneity (I^2 = 99%) around 2/3 of which was associated with baseline pain.[38] The authors note that MCID for chronic pain relief varied considerably among published studies and was influenced by the operational definition of relevant pain relief and clinical condition of participants in the studies.

The Agency for Healthcare Research and Quality (AHRQ) whose comprehensive evidence reviews are cited several times in this guideline has summarised their definitions for magnitude of effects in meta-analyses of chronic pain trials as follows:

- A small effect was defined for pain as a mean between-group difference following treatment of 0.5 to 1.0 points on a 0- to 10-point numeric rating scale or visual analog scale (VAS) and for function as a standardised mean difference (SMD) of 0.2 to 0.5 or a mean difference of 5 to 10 points on the 0 to 100-point Oswestry Disability Index (ODI), 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent.
- A moderate effect was defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS and for function as an SMD of 0.5 to 0.8, or a mean difference of 10 to 20 points on the ODI, 2 to 5 points on the RDQ, or equivalent.
- Large/substantial effects were defined as greater than moderate.

1.5 Statement of intent

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at through a process of shared decision making with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be documented in the patient's medical records at the time the relevant decision is taken.

1.5.1 Influence of financial and other interests

It has been recognised that financial or academic interests may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from these sources, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial and academic interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies of declaration of interests forms are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

1.5.2 Prescribing of licensed medicines outwith their marketing authorisation

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[39]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".[39]

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:[40]

- be satisfied that there is no suitably licensed medicine that will meet the patient's need
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so.
- make a clear, accurate and legible record of all medicines prescribed

and, when not following common practice, the reasons for prescribing an unlicensed medicine.

Non-medical and medical prescribers should ensure that they are familiar with the legislative framework and the Royal Pharmaceutical Society's Competency Framework for all Prescribers.[41]

Prior to any prescribing, the licensing status of a medication should be checked in the Summary of Product Characteristics (SmPc) (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[42]

1.5.3 Health technology assessment advice for NHSScotland

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly-licensed medicines, new formulations of existing medicines and new indications for established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

SMC advice relevant to this guideline is summarised in the section on implementation.

2 Opioids

2.1 Introduction

In recent decades there has been a significant increase in opioid prescribing for people living with chronic pain, despite limited evidence for long-term efficacy. There is international concern around the rise in opioid prescribing and opioid-associated mortality rates in the United States, Australia and Europe.[43-45] Opioid prescribing rate rises have been reflected in Scotland and England[46,47] with an increase between 2012 and 2016 followed by a gradual fall (excluding a slight increase during the COVID-19 pandemic).[48,49] Meanwhile, there has been growing awareness and concern about the harms caused by long-term use of opioids and their adverse effects.[50,51]

These concerns prompted the Faculty of Pain Medicine (Royal College of Anaesthetists) 'Opioids Aware' campaign, which provides evidence-based resources and advice for clinicians and patients on the use of opioids for pain (including chronic pain). In 2018 the International Association for the Study of Pain (IASP) produced a statement on the use of opioids in people with chronic pain, which concluded that, "There may be a role for medium-term, low-dose opioid therapy in carefully selected patients with chronic pain who can be managed in a monitored setting. However, with continuous longer-term use, tolerance, dependence and other adaptations compromise both efficacy and safety".[52] Evidence from the United States of America (USA) indicates that opioid use around the time of surgery (peri-operative opioid use) may have contributed to the large increase in prolonged opioid use.[53]

Opioids have been used for their analgesic effects for centuries. For the majority of clinically used opioids, this effect is predominantly, although not exclusively, via the mu opioid receptor (MOR). The potency of different opioids at this receptor varies. Some opioids, such as codeine, dihydrocodeine, tramadol and tapentadol, have defined upper dose limits in the British National Formulary (BNF). Among these, the BNF classifies codeine and dihydrocodeine as "weak opioids", with the other commonly-used opioids being classed as "strong opioids".[54] Tramadol and tapentadol have additional actions on pain systems through noradrenergic mechanisms; tramadol also acts through serotoninergic reuptake inhibition. These additional actions on pain systems may have advantages in some chronic pain conditions such as neuropathic or mixed pains, but they can also limit upward dose titration and increase the range of adverse effects. In 2014 tramadol was reclassified by the UK Government as a Schedule 3 controlled drug, and recategorised by the BNF as a strong opioid (despite its relatively low potency at MORs). Other strong opioids listed in the BNF include morphine, diamorphine, hydromorphone, oxycodone, fentanyl, buprenorphine and methadone.[54]

2.2 Evidence of benefit

Comparing opioids with placebo or non-opioids in terms of clinical effectiveness, there is high-quality evidence available, including a systematic review pooling data from 74 RCTs (20,502 participants),[55] a systematic review and network meta-analysis (NMA) pooling data from 82 RCTs (22,619 participants),[56] and several additional studies from surveillance to March 2022.[57-59]

There were no RCTs comparing opioids with placebo for longer than 6 months' follow up, and only one that compared opioids with non-opioids for up to one year's follow up.[60]

2.2.1 Opioids versus placebo

Comparing opioids with placebo, opioids were associated with a slightly lower pain intensity score (mean difference (MD) -0.79 on a scale from 0 to 10, 95% confidence interval [CI] -0.93 to -0.67; 71 trials, 19,616 participants).[55] This difference of less than 1 point on an 11-point scale is unlikely to be clinically significant. When only trials with 3 to 6 months' follow up were included, there was no difference in pain intensity between opioids and placebo (MD -0.30, 95% CI -0.83 to 0.23; 8 trials, 2,243 participants). When considering all studies regardless of follow-up duration, there was evidence of a pain response (typically defined as a 30% or great pain reduction, though definitions across studies varied) for opioids when compared with placebo (risk ratio (RR) 1.35, 95% CI 1.24 to 1.48; 44 trials, 12,481 participants). When restricted to studies with follow-up periods between 3 and 6 months, there was no significant difference in the likelihood of pain response from opioids compared with placebo (RR 1.19, 95% CI 0.68 to 2.17; 5 trials, 1,503 participants). There was high-quality evidence of better function and physical health status in the short term (1 to <6 months). Greater improvement in physical health status was seen with opioids (1.64/100, 95% CI 1.10 to 2.17; 23 trials, 8,005 participants) compared with placebo, although this improvement was small and not clinically significant, and there was no difference in mental health status (-0.48/100, 95% CI -1.39 to 0.44; 21 trials, 7,586 participants). No studies had longer than 6 months' follow up.	1++
Greater short-term benefit from opioids (versus placebo) has been reported for people with neuropathic pain (-1.15 points on an 11-point scale, 95% CI -1.43 to -0.91; 20 trials, 2,568 participants) compared to those with musculoskeletal pain (-0.67 point on an 11-point scale, 95% CI -0.81 to -0.54; 50 trials, 16,979 participants).[55] The difference of 0.48 points is statistically significant (p=0.009), although of uncertain clinical importance (*see section 1.4.1*). Although the difference in pain intensity reduction with enriched enrolment RCTs (which ensure that only responders who experience considerable pain relief and no or acceptable side effects on a predefined or titrated dose during a selection phase are included in the randomised double-blind experimental phase) compared with non-enriched enrolment RCTs was non-significant (-0.86 vs -0.75),	

the former resulted in a significantly lower relative risk of discontinuation due to adverse events (RR 1.35, 95% CI 1.02 to 1.78; 25 trials, 8,011 participants) compared with non-enriched RCT designs (RR 3.06, 95% CI 2.5 to 3.81; 36 trials, 11,983 participants, p<0.005).

A well conducted systematic review with NMA evaluated 14 opioids either against placebo or against each other.[56] Seventy-eight trials which included 21,906 participants reported on pain relief. Using the surface under the cumulative ranking curve (SUCRA) rankings suggested that modified-release (MR) codeine, MR oxymorphone, and immediate-release (IR) oxycodone were the best opioids for pain relief with reduction in pain scores ranging from 0.99 to 2.03 cm on a 10 cm scale but these findings were supported by evidence rated low to very low certainty.

Sufficient relevance, sufficient credibility

There was high to moderate certainty evidence that IR tramadol, MR morphine, sublingual buprenorphine, MR tapentadol, and MR tramadol were superior to placebo, with pain reduction ranging from 0.8 to 1.09 cm on a 10 cm scale.

For physical function, the evidence (39 studies, 13,134 participants) was rated low to very low quality and according to the SUCRA rankings the most effective opioids for improving function were MR codeine and MR hydromorphone.

2.2.2 Opioids versus non-opioid medication

Comparing opioids with non-opioids (medications used across trials included non-steroidal anti-inflammatory drugs (NSAIDs), antiarrhythmic drugs, anticonvulsants and antidepressants), no difference in terms of pain reduction was observed (MD -0.29 on a 0 to 10 scale, 95% CI -0.61 to 0.03) at short-term follow up (1 to <6 months; 14 trials, 2,195 participants), nor for likelihood of a pain response (RR 1.28, 95% CI 0.90 to 1.85; 12 trials, 2,886 participants).[55]

1++

For effects on functional ability, pooled analysis of 11 RCTs which included 2,010 participants found that there was no difference in functional ability between opioids and non-opioids (standardised mean difference (SMD) 0.00, 95% CI -0.14 to 0.12).

No data was reported on quality of life in studies comparing opioids versus non-opioid use. Only one study, the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial,[60] which followed participants up for longer than 6 months, was identified in meta-analyses.[55] The trial compared outcomes in 106 people with chronic musculoskeletal pain who received opioids with 115 receiving non-opioid medicines and found no difference in function between the groups, but a greater reduction in pain severity among those receiving opioids (4.0/10 vs 3.5/10) at 12 months. The size of this effect did not meet the minimal clinically important difference (MCID) established by the trial authors (*see section 1.4.1*).

2.2.3 Summary of effectiveness

Evidence based on high-quality systematic reviews consistently found little or no reduction in pain severity among people with chronic pain who were

treated with opioids, compared with placebo or non-opioid medications. Where improvements in pain severity and function were seen with opioids, these were small and not clinically significant, and there was no evidence of opioid efficacy when treatment was given beyond 3 months.

Taking into account the low certainty of evidence alongside the calculated rankings of relative efficacy from the NMA supports the assertion that individual opioids are similarly effective with no opioid showing superior short-term effectiveness.

2.3 Evidence of harms

2.3.1 Opioids versus placebo

Opioids were associated with a greater risk (RR 2.25, 95% CI 1.86 to 2.73; 61 trials, n=19,994 participants) of study discontinuation due to adverse events compared with placebo. There were significantly greater risks of all recorded adverse events (nausea, vomiting, constipation, somnolence, dizziness, pruritus), except for headache (no difference) at short-term follow up.[55] 1++

In the NMA, 53 studies (n=20,283) reported on vomiting. The highest certainty of evidence was for MR oxycodone which was found to result in greater risk of vomiting than placebo with an odds ratio of 7.12 (95% CI 5.42 to 9.35). Analysis of 67 trials with 22,681 participants provided high to moderate certainty evidence that MR oxycodone, MR tramadol and MR tapentadol resulted in increased nausea compared with placebo. Analysis of 64 studies with 22,531 participants provided high to moderate certainty evidence that MR oxycodone, MR hydromorphone, and MR tramadol resulted in increased risk of constipation compared with placebo.[56] Sufficient relevance, sufficient credibility

2.3.2 Opioids versus non-opioid medication

Pooled analysis of 12 RCTs with 3,637 participants found that opioids were more likely than non-opioids to be associated with discontinuation due to adverse events (RR 2.18, 95% CI 1.48 to 3.08; moderate certainty of evidence). The most common adverse events were vomiting, pruritis, constipation, nausea, drowsiness and headache. Risk of adverse events/drug reactions and discontinuation did not differ between low and high opioid doses. There were also associations between opioid use and fractures, falls, cardiovascular events, and endocrine outcomes, but not with self harm.[55] 1++

2.3.3 Other evidence

No systematic review of RCTs has identified studies that investigate the long-term (>12 months) adverse effects of opioids. Observational studies found that, compared with people taking opioids, people not taking opioids were more likely to report lower pain intensity at one year,[55] and were less likely to experience severe pain-related interference with activities at two years.[61] The SPACE trial, that followed participants up for 12 months found that those receiving opioids experienced more (1.8 vs 0.9), and more

frequent (p=0.03) medication-related symptoms than those receiving non-opioid medicines.[60]

A systematic review and its associated surveillance reports noted consistent evidence from observational studies of associations between increasing opioid dose and increasing risk of overdose and opioid-related mortality.[57] Similarly, observational studies report a dose-dependent association between opioid prescription and opioid use disorder (OUD), with both a higher daily dose, and, particularly, a longer duration of therapy associated with a greater risk of subsequent OUD. One case-control study reported that doses of opioids greater than 20 mg MED/day taken by drivers were associated with increased odds of injuries related to road trauma.[55]

2++ (evidence level limited to studies used in this analysis)

A 10-year longitudinal study followed up over one million adults (mostly in the UK) who were prescribed opioids for non-cancer pain. They found that UK adults who were prescribed morphine had a 12-fold risk of all-cause mortality compared with those who had been prescribed codeine (hazard ratio (HR) 12.58, 95% CI 11.87 to 13.32). This risk was dose dependent, and rose with age. All-cause mortality risk was greater among those prescribed >50 mg/day morphine equivalent dose (MED), and in the presence of multimorbidity and/or a history of substance misuse.[62]

2+

A systematic review of studies involving individuals treated with opioids for chronic non-malignant pain (148 studies, >4.3 million participants) reported that 9.3% experienced dependence and opioid use disorder (D&OUD), with a further 12.4% at risk of this, and a total of 29.6% showing signs and symptoms of D&OUD.[63]

The authors of a large systematic review with meta-analysis of opioid treatments for chronic pain noted that most trials excluded people with substance use history or mental health disorders or did not describe these characteristics, meaning that differential effects according to comorbidities could not be assessed.[55] However, they identified a large UK cohort study estimating risk of overdose (98,140 participants) which reported a dose-dependent increase of hazard ratio for overdose (≥50 mg morphine-equivalent dose (MED)/day compared with no opioid (HR 3.81, 95% CI 2.50 to 5.80).[64]

2++ (evidence level limited to studies used in this analysis)

Although screening tools exist to predict D&OUD, evidence for their effectiveness is weak, and their effect size has been modest at best. A systematic review identified no reliable evidence for the effectiveness for the use of urine drug screening, pill counts or prescription drug monitoring programmes to predict subsequent misuse.[65]

There is therefore consistent evidence of adverse events associated with opioid treatment, and this association appears to be dose dependent.

2.4 Summary of benefits and harms of opioids for chronic pain

There may be limited short-term benefits in pain intensity and some aspects of function associated with short-term use of opioids. These benefits appear to be small and to reduce or disappear with longer-term

use (beyond 3 months). The possibility that some people who use opioids may experience greater short-term benefits cannot be excluded. This suggests that individualised treatment may be considered. There is no evidence suggesting that opioids may be more effective than a placebo after six months, and some evidence suggesting that pain-related and functional outcomes may be worse with long-term (>12 months) opioid use, compared with not taking opioids.

There are strong associations between opioid therapy and adverse effects (minor and serious), with approximately two- to threefold greater relative risk of specific adverse events (gastrointestinal symptoms, drowsiness, dizziness, and itching) versus placebo. Observational evidence consistently shows dose-dependent associations between opioid therapy and subsequent opioid use disorder, overdose and death, as well as evidence that taking opioids for longer duration is associated with opioid use disorder.

2.5 Other factors

2.5.1 Prescribing opioids

The evidence suggests that for most people with chronic non-cancer pain, opioid treatment provides minimal-to-no benefit and is likely outweighed by adverse effects, especially after three months, in terms of both pain intensity and overall function. In most people presenting with chronic non-malignant pain, therefore, opioids are unlikely to be appropriate. Certainly, nothing other than short-term (<3 months) use should be considered unless there is clear evidence of benefits outweighing actual or potential harm beyond three months. Any prescribing should be accompanied by early and frequent review to minimise harms and optimise duration of treatment for maximum benefit.

If a trial of an opioid is considered, then measurable treatment goals should be agreed between clinician and person with chronic pain before opioids are started and an exit strategy put in place if these goals are not achieved.[66] This will need a comprehensive biopsychosocial assessment, and consideration of personal goals, knowledge, previous experience and preferences. Shared decision-making will be important, involving individuals, families and carers as well as the healthcare team. This will need to deploy the evidence that is available, and with educational material such as that which will accompany this guideline, and that already available through Opioids Aware. The lack of good evidence for specific risk prediction tools means that clinical judgment, based on this assessment, discussion and information, is important from the outset.

People who are already being prescribed long-term opioids will need separate consideration, and assessment of benefits (pain reduction, function, quality of life) and harms, potentially with a view to safe reduction and withdrawal of treatment, if appropriate.[67] It will be important to consider the possibility of stigmatising people who have been taking opioids on long-term prescription, and to avoid this.

The following recommendations are based on high-level evidence (for limited clinical effectiveness and risk of adverse events/drug reaction) during the first six months, and on low-level evidence after six months and regarding the risk of overdose and other adverse events. These recommendations cover both IR and MR opioids.

R **Opioids should not be considered routinely for people with chronic non-malignant pain. In carefully selected individuals, when other therapies have been fully explored, opioids can be considered for short-term treatment (up to 3 months), if it is considered that the potential benefits outweigh the risks of serious harms such as addiction, overdose and death.**

R **After prescribing opioids, clinicians should undertake early and frequent review to identify any benefits and potential or actual adverse events/drug reactions, with a view to adjusting the dose or stopping the prescription when benefits cease or when adverse events occur.**

R **All people receiving opioid doses of >50 mg MED/day should be reviewed regularly (at least annually) to detect emerging harms and consider ongoing effectiveness. Pain specialist advice or review should be sought at doses >90 mg MED/day.**

✓ For people who are already on long-term opioids, clinicians should consider reviewing them to assess benefits and potential or actual harms, with a view to reducing or stopping the prescription.

3 Naloxone

3.1 Introduction

Naloxone is an opioid antagonist which can be used to temporarily reverse the central nervous system (CNS) and respiratory depressant effects of an opioid overdose. Naloxone is licenced for lay administration in the event of a suspected opioid overdose; legislation allows for anyone to administer naloxone for the purpose of saving a life.

Naloxone is a prescription- only medicine, however specific legislation is in place within the UK that allows the supply of intramuscular and intranasal formulations to people at risk of an opioid overdose without the need for a prescription, under certain circumstances.

A national naloxone programme was established in Scotland in 2011 in response to increasing numbers of drug-related deaths. After training, naloxone kits suitable for community administration are supplied to people at risk of opioid overdose, their friends, family and service workers to help reduce drug-related deaths in Scotland. During Quarter 3 2023/24 there were 7,589 naloxone kits issued across Scotland.

Whilst the supply of naloxone has been successfully established in Scotland the focus of the programme is to target those at increased risk of opioid overdose due to substance misuse. Current practice in Scotland does not proactively identify people who are prescribed opioids for chronic pain who may be at an increased risk of opioid overdose (See section 2.3.3).

This section of the guideline assesses current evidence on whether naloxone should be co-prescribed when opioids are used for chronic pain (or when long-term/high dose opioids are prescribed)

3.2 Evidence of benefit

There is limited evidence around the coprescribing of naloxone when opioids are indicated for chronic pain. Only one observational study, which was rated at acceptable quality, was identified that investigated coprescribing of naloxone when opioids are indicated for chronic pain (or when long-term/high-dose opioids are prescribed).[68]

The observational study assessed the association between coprescribing of intranasal naloxone for people taking daily opioids for chronic pain and the use of emergency departments (ED) in a safety-net healthcare setting in the USA.[68] Safety-net hospitals provide healthcare for individuals regardless of their insurance status or ability to pay. These hospitals typically serve a proportionately higher number of uninsured, low-income, and other vulnerable individuals. Whilst, in Scotland, the risk of being prescribed an opioid is higher in areas of high deprivation,[47] differences in the healthcare systems and other sociodemographic factors may make this study population less representative of the Scottish target population. 2+

The mean age of the study participants was 56.7 years (± 10.8), 58.6%

were male, and the majority of patients were black. The most commonly prescribed opioid was oxycodone and the median dose 53 mg MED/day. The study does not provide any information regarding comorbidities or polypharmacy within this population. Notably they were not able to determine whether the patients included in the analysis had any history of substance use, however, people taking opioids for opioid use disorder at the time of the study were excluded.

The observational study suggested benefit in coprescribing naloxone when opioids are indicated for chronic pain. The study found that, on average, coprescribing naloxone was associated with 6% fewer ED visits per month (incidence rate ratio (IRR) 0.94, 95% CI 0.89 to 0.998, p=0.044), a 47% reduction in ED visits per month after 6 months (IRR 0.53, 95% CI 0.34 to 0.83, p=0.005) and 63% reduction after one year (IRR 0.37, 95% CI 0.22 to 0.64, p<0.001).

When advised to offer naloxone to all people receiving long-term opioids, clinicians were found to be more likely to prescribe naloxone to those whom they considered to be at higher risk for opioid overdose, including individuals receiving higher doses of opioids and those who had previously had an opioid-related ED admission. There is no information about whether naloxone prescribed was actually dispensed, and no investigation of outcomes other than ED attendance.

3.3 Evidence of harms

The study hypothesises that prescribing naloxone may change patient behaviour with respect to opioids. However, the authors also caution that there may be hazards to risk stratifying users of opioids to be offered naloxone, including stigma and concerns about identifying an individual's elevated risk for overdose.

3.4 Summary of benefits and harms of naloxone coprescription with opioids for chronic pain

There is limited evidence to support widespread coprescribing of naloxone to people prescribed opioids for chronic pain. However, learning from other at-risk groups should be applied and where additional risk factors for opioid overdose are identified clinicians should consider offering naloxone in a suitable "take home" formulation.

3.5 Other factors

Public Health Scotland has reported that the supply of naloxone for use in the community is feasible in the Scottish context as it is already established for other at-risk groups, such as those receiving opiate substitution treatment.

When considering overdose risk among people who misuse drugs, additional risk factors are identified as a history of opioid-related hospital admissions, previous near-fatal overdoses, a history of substance use (including alcohol), coprescribing of depressant medicines, high-dose

opioid prescribing, and multimorbidity that increases the risk of opioid toxicity (see section 2.3.3).[69,70]

It is recognised as good practice to offer training to people who are prescribed opioids for chronic pain and significant others to recognise the signs of an opioid overdose and appropriate intervention, including naloxone administration.[66]

R **Clinicians should consider prescribing naloxone for people with chronic pain who are prescribed opioids and who may be at risk of an opioid overdose.**

✓ Offer a naloxone product that is suitable for use in the community, for example, an intranasal formulation or prefilled syringe.

4 Medicinal cannabis

4.1 Introduction

There is a need for new, effective, safe pharmacotherapy for long-term management of chronic pain. Since the original guidelines were published in 2013, a number of medicinal cannabis products have become available, with an evolving evidence base around their use in chronic pain management. Anecdotal evidence from patients, and historical reports of cannabis use do indicate a potential analgesic effect. The hemp plant, *Cannabis sativa* (marijuana), produces up to 60 cannabinoid derivatives, of which delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are best known, with medicinal products available containing these compounds.[71] There is a potential neurobiological basis for analgesic effects of cannabinoids, with preclinical evidence of antinociception, through the endocannabinoid system, mediated by G-protein-coupled cannabinoid receptors (CB1 and CB2) found in the peripheral and central nervous system (PNS, CNS). CB1 is expressed in the PNS and CNS, with psychoactive effects from central activation, as seen with THC. CB2 receptors are mainly found in the periphery (eg immune system) with some expression in the brain. Both receptors may have a role in nociception, including in chronic pain models.[72-74]

It is important to understand the evidence for analgesic use of medicinal cannabis, and any related implications for clinical practice, particularly safety issues, with long-term use. It is essential to avoid a situation such as that which occurred with opioids which were used widely for chronic pain management despite limited evidence of long-term effectiveness and accumulating evidence of major harms (see section 2). For new classes of analgesic drugs, such as cannabinoids, where long-term use is likely, a robust evidence base is needed to support any strong recommendations for clinical use.

Currently in Scotland, although there is no preparation licensed for treatment of chronic pain, delta-9-tetrahydrocannabinol and cannabidiol (Sativex®) is accepted for use within NHSScotland as treatment for symptom improvement in adults with moderate to severe spasticity due to multiple sclerosis, who have not responded adequately to other antispasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.[75] Any use for chronic pain would therefore be off label. National Institute for Health and Care Excellence (NICE) guideline 144 on cannabis-based medicinal products did not recommend the use of cannabinoids for the treatment of chronic pain, unless within the context of a clinical trial.[76] Subsequent to this, position statements from the Faculty of Pain Medicine (Royal College of Anaesthetists, London),[77] and the IASP (after a comprehensive evidence review for chronic pain)[78] did not recommend use for chronic pain due to the lack of high-quality evidence for efficacy and safety, particularly with long-term use. The need for robust clinical trials was highlighted by both organisations, as well as the use of regulatory

standards to ensure safety.

4.2 Evidence of benefit

There was a reasonable quantity of evidence on which to base conclusions (subject to significant limitations around quality and risk of bias of studies included in systematic reviews). Thirteen systematic reviews with meta-analyses, and one NMA were identified published between 2018 and 2023.[79-92] The number of included RCTs in the systematic reviews ranged from 8[83] to 65[79] (90 from the NMA comparing cannabinoids to opioids or placebo),[84] with 6[80] to 57[89] observational studies. As would be expected, there was considerable overlap of included studies across the reviews. Four of the reviews focussed specifically on chronic neuropathic pain. The majority of the reviews (11/13) were rated as high quality, two acceptable quality, and the NMA was rated as sufficient. Overall, the quality of the studies included in the systematic reviews was mainly very low to low, with a high (or unclear) risk of bias, making our confidence in the conclusions less than if the included studies were of consistently high quality.

1++
1+

4.2.1 Pain severity

In the majority of the reviews (10/13), small reductions in pain were reported compared with placebo, to a level unlikely to be of clinical significance (*see section 1.4.1*). Three reviews reported no statistically significant improvement in pain. In the NMA (up to 84 RCTs included 19,693 participants) cannabis reduced pain on a 0-10 scale, to a similar (small) extent as to that seen with opioids, with a weighted mean difference (WMD) 0.23 (-0.06 to 0.53).[84] Although cannabinoids were compared with opioids in the NMA, most comparisons were indirect, with the only RCT directly comparing an opioid (dihydrocodeine) to a cannabinoid (nabilone) finding a statistically significant improvement in pain severity for dihydrocodeine compared with nabilone in people with neuropathic pain.[93]

1++, Sufficient relevance, sufficient credibility

In a high-quality living systematic review and meta-analysis (minimum of one month of follow up), a number of different preparations were included, with a reported mean difference (MD) in pain severity (0–10 scale) ranging from -0.54 (95% CI -0.95 to -0.19; 7 trials, 702 participants) to -1.97 (95% CI -5.91 to 1.21; 2 trials, 294 participants) for cannabis products compared with placebo).[81]

1++

Meta-analysis of longer-term observational studies (up to 12 months) found that reductions in pain intensity did not meet predefined criteria of clinical significance with a WMD of pain intensity reduction of 1.75 (95% CI 0.72 to 2.78; 6 trials, 2,571 participants) on a 0–10 scale, compared with placebo,[80] with a further meta-analysis finding no evidence of sustained benefit in terms of reduced pain intensity, beyond 6 months.[81]

2++

None of the four systematic reviews that focussed on chronic neuropathic pain, found a clinically significant reduction in pain severity (SMD -0.26, 95% CI -0.42 to -0.10; 9 trials, 1,289 participants),[82] SMD -0.44 (95% CI -0.69 to 0.19; 8 trials, 893 participants),[86] (SMD -0.35 (-0.60 to -0.09; 14

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1+

trials, 1,837 participants),[87] and MDs (0–100 scale) ranging from -6.62 (95% CI -9.15 to -4.09; 5 trials, 552 participants) for THC/CBD to -8.68 (-10.97 to -6.38; 7 trials, 332 participants) for THC[88] with a calculated number-needed to treat of 20 (11–100) for one person to benefit from a 50% reduction in pain.[87]

4.2.2 Function, quality of life and sleep

Seven systematic reviews[79-81,84,88-90] reported on the effect of cannabinoids on functional abilities (eg physical, emotional, social), with three of those finding very small to small benefits for physical function for cannabinoids compared with placebo. For example, one review found a MD (0–10 scale) ranging from -0.42 (95% CI -0.73 to -0.16; 6 trials, 616 participants) to 1.75 (95% CI -0.46 to 3.98; 1 trial, 16 participants) for function for cannabis-based products compared with placebo, depending on the formulation of the cannabinoid.[81] A further review found a WMD of 2.52 (95% CI 0.37 to 4.91; 44 trials, 12,727 participants) for cannabis compared with placebo (0–100 scale, SF-36).[84] A systematic review of observational studies found moderate benefits of cannabis on disability compared with placebo (fair-quality evidence), with a SMD 0.45 (95% CI 0.05 to 0.88; 5 trials, 2,201 participants).[80] There was a little effect of cannabis compared to opioids for physical functioning, with a WMD 0.47 (95% CI -1.97 to 2.99; 44 trials, 12,727 participants) on a 0–100 scale (SF-36).[84]

1++
1+
2++
Sufficient relevance, sufficient credibility

Evidence on Quality of Life (QoL) was inconsistent, with either minor benefits (one study)[80] or no benefit (6 studies)[79,81,83,86-88] reported when compared with placebo, with low-quality evidence.

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1+
2++

For people experiencing neuropathic pain, there was a small, but statistically significant improvement in sleep quality (SMD 0.40, 95% CI 0.19 to 0.61; 6 trials, 744 participants (0–10 scale)) in the one review where sleep quality was a primary outcome. However, there were also increases in daytime somnolence (SMD 2.23, 95% CI 1.32 to 3.74; 7 trials, 867 participants), nausea (OR 1.66, 95% CI 1.22 to 2.27; 7 trials, 867 participants) and dizziness (OR 3.80, 95% CI 2.52 to 5.73;7 trials, 867 participants).[86]

1++

4.3 Evidence of harms

There was consistent reporting of an increase in adverse effects for cannabinoids compared with placebo at levels likely to be of clinical significance. Adverse effects described were extensive, and included sedation, daytime somnolence, anxiety, mood disorder, suicidal thoughts and nausea/vomiting.

One systematic review reported relative risk (RR) for dizziness ranging from 2.52 (95% CI 1.20 to 4.82) to 8.34 (95% CI 4.53 to 15.34); and RR for sedation from 1.60 (95% CI 1.01 to 2.95) to 5.04 (95% CI 2.10 to 11.89), for different cannabinoids compared with placebo.[81]

1++

In a further systematic review, pooled event rates for all-cause adverse events were 81.2% for cannabinoids compared with 66.2% for placebo,

1++

with a number needed to harm (NNTH) of 6 (95% CI 5 to 8; 10 trials, 1,959 participants).[89] A Cochrane review of neuropathic pain found that nervous system adverse events were higher in people receiving cannabis-based medication compared with placebo (61% vs 29%, Risk Difference 0.38 (95% CI 0.18 to 0.58; 9 trials, 1,304 participants)).[87] One high-quality review of 39 observational studies which included 12,143 participants, median duration 24 weeks (interquartile range 12 to 33.8 weeks)),[92] used long-term and serious harms from cannabinoids as the primary outcome. Prevalence of any adverse events was 26% (95% CI 13.2% to 41.2%) with a prevalence of psychiatric adverse events of 13.5% (95% CI 2.6% to 30.6%). Evidence was of low quality, with high risk of bias. Prevalence of serious adverse events was lower at 1.2% (95% CI 0.1 to 3.1) with very low-quality evidence.

Four systematic reviews specifically considered dependence or psychosis as secondary outcomes.[79,80,87,94] One review identified a single 32-week open-label extension study (n=124) where one participant displayed mild signs of cannabis dependence. There was no other evidence reported in any of the other studies on dependence. Many of the studies in the systematic reviews excluded people with dependence/substance use issues, or psychosis/ severe mental health problems. 1++

4.4 Summary of benefits and harms of medicinal cannabis for chronic pain

In conclusion, although there were some statistically significant small reductions in pain severity, there was no strong evidence of clinically relevant pain reduction for cannabinoids. Overall, there was no improvement in quality of life, or clinically significant improvement in function. Whilst one review found a small improvement in sleep quality there was also an increase in daytime somnolence and other adverse effects.

The evidence for increased adverse effects/ harms for cannabinoids compared with placebo was consistent (in all the reviews which reported on this (except one[82]), with generally much larger effect sizes than found for any benefits. A wide range of harms were reported, (even in short- to medium-term studies) including sedation, anxiety, dizziness and nausea. There was insufficient evidence to comment on long-term dependence or mental health issues.

While the systematic reviews were mainly of high quality, the included studies had limitations in quality and risk of bias.

4.5 Other factors

Whilst there are a considerable number of clinical studies on medicinal cannabis, from a broad geographical area, and a range of research groups/ institutions, there are a number of major limitations with these studies, including:

- Duration: The majority of the studies included in the reviews were of short duration, with only six observational studies identified that had 1++ 1+

follow up for >6 months and the majority of RCTs having follow up for <6 months. As chronic pain is a long-term condition, longer term follow up is needed to ensure studies reflect the clinical population.

- Comorbidities were not consistently reported, with many of the studies identified in the systematic reviews excluding people with a history of substance use, and major medical diseases, including mental health conditions. Reporting on dependency and substance use was limited, and often not specifically reported.
- Risk of bias, where assessed, was moderate to high, and study quality was very low to low in the majority of studies included in the systematic reviews. All the authors of one systematic review on neuropathic pain declared links with the manufacturers of nabiximols.[82] Of the 16 studies included in the Cochrane review on cannabis in neuropathic pain, 12 declared potential conflicts or funding from the manufacturers of the studied drugs.[87] There was overlap of inclusion of these studies with other systematic reviews.
- Only two of the reviews specifically mentioned input from people with lived experience, who were included on the guideline panels.[90,92]

R **Medicinal cannabis-based products are not recommended for routine use in the management of chronic pain. This takes into consideration the very limited evidence of clinically significant improvements in pain or wider impact (function/ QoL), combined with consistent evidence of adverse effects/ harms.**

5 Antidepressants

5.1 Introduction

Chronic pain is common in adults and can negatively impact upon physical ability, wellbeing, and quality of life.[95,96] Antidepressants have been used in the management of some chronic pain conditions, with mixed evidence of benefit for pain reduction and patient-reported efficacy.[97,98]

Depression and chronic pain are often interconnected, with pain symptoms worsening depression and depression causing pain and many symptoms overlapping within these clinical diagnoses (for example, fatigue and loss of motivation or pleasure in activities).

Antidepressants are indicated for treatment of depression but are often used off-label in the management of other conditions. Antidepressant medications may relieve both pain and depression through shared neurotransmitter pathways in the brain, hence there may be individuals with undiagnosed or unrecognised mood disorders where the beneficial effect on pain may be mediated by improvement in mood. Evidence-based guidelines, including from NICE and SIGN, have recommended a range of antidepressants for different populations with chronic pain.[99-102]

In Scotland, antidepressants, particularly amitriptyline and other tricyclic antidepressants are frequently used as first-line agents in the treatment of chronic pain conditions, particularly neuropathic pain, fibromyalgia-type conditions and general chronic musculoskeletal type conditions such as mechanical low back pain.

5.2 Evidence of benefit

A large Cochrane NMA assessed the effectiveness and safety of antidepressants compared with placebo or any active comparator for pain management and included 176 RCTs involving 28,644 adult participants (mean age 50.6 years, 68.3% were female) with fibromyalgia, neuropathic pain, musculoskeletal or other types of chronic pain. Study duration ranged from two weeks to nine months, with an average duration of 10 weeks. Only six of the 176 trials included long-term follow-up data and the authors were unable to draw any conclusions on the long-term efficacy or safety of antidepressants. It is worth noting that the NMA includes some studies of medications which are not available in the UK.[103]

Primary outcomes of benefit were substantial (50%) reduction in pain, pain intensity, and mood. Secondary outcomes were moderate reduction in pain (30%), physical function, sleep, quality of life, Patient Global Impression of Change (PGIC), serious adverse events, and withdrawal.

Sufficient relevance, sufficient credibility

While study populations were similar to the target populations in Scotland, the authors note that most studies did not include people with anxiety or depression. All results and rankings were based on comparison of each antidepressant with placebo.

Duloxetine was consistently the highest-ranked antidepressant for pain

relief, pain intensity, physical function and quality of life outcomes (although not significantly different from placebo in terms of quality of life). Both standard and high-dose duloxetine were equally effective for most outcomes. Milnacipran was often ranked second among the antidepressants, although the certainty of evidence was lower than for duloxetine. There was insufficient evidence to draw conclusions about the effectiveness or safety of any other antidepressant.

Compared with placebo, standard-dose (60 mg) duloxetine showed a small to moderate effect on substantial pain relief (odds ratio (OR) 1.91, 95% CI 1.69 to 2.17; 16 studies, 4,490 participants, moderate-certainty evidence) and pain intensity (SMD -0.31, 95% CI -0.39 to -0.24; 18 studies, 4,959 participants, moderate-certainty evidence). High-dose (>100 mg) milnacipran had a small effect on substantial pain relief (OR 1.72, 95% CI 1.13 to 2.62; 1 study, 384 participants, low-certainty evidence). Standard-dose (100 mg) milnacipran had a small effect on pain intensity (SMD -0.22, 95% CI -0.39 to 0.06; 4 studies, 1,866 participants, moderate-certainty evidence).

Duloxetine (OR 1,79, 95% CI 1.67 to 1.91; 24 studies, 7,833 participants, moderate-certainty evidence) and milnacipran (OR 1.70, 95% CI 1.48 to 1.92; 7 studies, 3,056 participants, moderate-certainty evidence) had a small effect on moderate pain relief. Standard-dose duloxetine (SMD -0.24, 95% CI -0.32 to -0.18; 15 studies, 3,887 participants, high-certainty evidence), high-dose (>60 mg) duloxetine (SMD -0.23, 95% CI 0.30 to 0.16; 13 studies, 3,503 participants, moderate-certainty evidence) and standard-dose milnacipran (SMD -0.18, 95% CI -0.30 to -0.07; 3 studies, 1,840 participants, moderate-certainty evidence) had small effects on physical function. No antidepressant showed a significant effect on quality of life (low- or very low-certainty evidence).

Due to small sample sizes and network sparseness the authors were unable to analyse results across different pain conditions but note that there is no high-quality or high-certainty evidence for the efficacy of amitriptyline, desipramine, desvenlafaxine, imipramine, mirtazapine, nortriptyline, or venlafaxine for any of the included outcomes. They note that this aligns with previous systematic reviews in participants with neuropathic pain which showed no high-quality evidence for the efficacy of amitriptyline, desipramine, imipramine, milnacipran, nortriptyline, or venlafaxine[104-109] but moderate-quality evidence that duloxetine is effective for people with diabetic peripheral neuropathy.[97] For people with fibromyalgia, systematic reviews have reported no unbiased evidence that amitriptyline, desvenlafaxine, venlafaxine, or SSRIs were better than placebo,[110,111] and low-certainty evidence that duloxetine, milnacipran, and mirtazapine may yield moderate pain relief.[111] The authors suggest that the previous literature is mixed on the efficacy of antidepressants for musculoskeletal pain.[103]

5.3 Evidence of harms

Adverse events were recorded as a primary outcome of harm, while

secondary outcomes included serious adverse events, and withdrawal.

The NMA was unable to draw any conclusions about the safety of antidepressants for treating chronic pain because adverse event data were sparse and studies were underpowered to detect them. Adverse event rates for the highest-ranked antidepressants (desvenlafaxine and mirtazapine) were not significantly different from placebo but were based on results from only two studies each. Standard- and high-dose duloxetine and standard-dose milnacipran were equally ranked.[103]

Low-dose (<60 mg) duloxetine, high-dose milnacipran, standard-dose (25-75 mg) amitriptyline, and standard-dose (4-8 mg) esreboxetine were the lowest-ranked antidepressants, and people taking each of these drugs had more than double the odds of reporting an adverse effect compared with people receiving placebo.

Sufficient relevance, sufficient credibility

No antidepressants showed any significant difference for the outcome of serious adverse events when compared with placebo, and the confidence intervals were very wide.

Nortriptyline, mirtazapine, amitriptyline, desvenlafaxine, and venlafaxine all showed no significant difference compared with placebo for withdrawal. Duloxetine, milnacipran, esreboxetine, desipramine, and paroxetine all showed significant effects, ranging from small to moderate. The authors note that conclusions on the ranking of the individual drugs for this outcome were unreliable due to all antidepressants having wide and overlapping credible intervals.

All safety evidence had very low certainty.

Physiological or psychological drug dependency were not assessed in the NMA, although it is possible they were considered as adverse events.

5.4 Summary of benefits and harms of antidepressants for chronic pain

The NMA results and rankings are limited to comparisons of each antidepressant with placebo. There are no head-to-head comparisons of antidepressants reported. This is probably because of the size and complexity of the network. In some analyses in the NMA, pharmacological interventions were split into dose categories (low, standard and high) to address between-study heterogeneity.

Duloxetine probably has a moderate effect on reducing pain and improving physical function in the short term, with no evidence of longer term effects. Higher doses of duloxetine probably provide no extra benefits than standard doses. Milnacipran may reduce pain but had a smaller effect and was supported by less evidence. It is not possible to draw conclusions about the effectiveness of any other antidepressant. There was very low certainty evidence for all safety outcomes for all antidepressants and it is not possible to draw conclusions about the safety of any antidepressant prescribed for the management of chronic pain.

5.5 Other factors

Historically, antidepressants have been used to manage chronic pain conditions with tricyclic antidepressants (TCAs), commonly recommended as a treatment option for chronic pain. Most of the studies from which these recommendations were derived were small and not adequately powered.

However, there is also a lack of evidence to suggest that antidepressants have no value as a treatment option for some people who continue to experience chronic pain symptoms and clinicians should consider each person in their individual circumstances and chronic pain experience.

The use of duloxetine as a treatment option for patients with chronic pain in Scotland is feasible. Prescribers should be aware that the Scottish Medicines Consortium has accepted duloxetine for restricted use for the treatment of diabetic peripheral neuropathic pain in adults as second or third-line therapy (see section 10.4).

Milnacipram is not routinely available in the UK.

R **Clinicians should consider a trial of 60 mg duloxetine in people with chronic pain which is not adequately managed by analgesics.**

Adopting a person-centred approach is critical. Pain is a very individual experience, and certain medications may work for people at an individual level even while the research evidence at population level is inconclusive or unavailable.

✓ Prescribers should engage in shared decision-making conversations and codevelop a management plan in partnership with the individual.

6 Pain management programmes

6.1 Introduction

Pain Management Programmes (PMPs) are a fundamental resource provided by secondary care pain services within NHSScotland. They exist as an intervention of choice when there is significant impact on physical, psychological or social function associated with chronic pain.[100]

Pain Management Programmes involve multidisciplinary working between various professionals – often physiotherapists, occupational therapists, clinical nurse specialists, psychologists and specialist doctors. Typically, this exists within secondary care settings and are deemed Comprehensive Pain Management Programmes (CPMPs). Integrated Pain Management Programmes (IPMPs) may also exist when the service is provided within primary care.[112] The guideline development group were not aware of any IPMPs operating within pain services in Scotland.

PMPs often consist of methods that promote long-term behavioural change. This may include methods based on cognitive behavioural therapy (CBT), acceptance-based methods, mindfulness, skills training, physical exercise and education. This is highly person-centred and tailored to each participants ability and social context. These skills are then taken home and integrated into daily routine. Generally, but not exclusively, PMPs are provided in a group format.[112]

Currently, the demand for Pain Management Programmes is high. They require significant resources given the number of healthcare professionals involved, and the time taken per patient.[113] It is imperative to assess their effectiveness on up-to-date evidence review and ensure adequate value for users of services within NHSScotland.

Within research, the guideline development group (GDG) recognises that PMPs are often treated as simple, one-off interventions, and the outcome measures used are comparable to those used to evaluate the effect of pharmacological treatments. In practice, PMPs are designed to improve quality of life in the presence of persistent pain.[112] Benefits that patients report, or alternative outcomes, following completion of a PMP are not always reflected in changes in the outcome measures used in published research. Addressing some of these questions and finding gaps in the measured outcomes was felt an important part of this review.

6.2 Definitions

A range of definitions of PMPs is available.

The British Pain Society defines the aims, methods and delivery of Pain Management Programmes within the UK. They consider a PMP to be a "group treatment which uses education and practice sessions to help people with chronic pain to manage their pain and everyday activities better… usually will have a psychologist and a physiotherapist providing most of the sessions and other staff such as occupational therapists,

nurses and doctors are often involved".[114] They note that PMPs aim to improve the life experience, emotional wellbeing, activity levels, coping and self efficacy of those living with pain.

The IASP, whilst not using the term PMP, defines interdisciplinary treatment as "Multimodal treatment provided by a multidisciplinary team collaborating in assessment and treatment using a shared biopsychosocial model and goals. For example: the prescription of an antidepressant by a physician alongside exercise treatment from a physiotherapist, and cognitive behavioural treatment by a psychologist, all working closely together with regular team meetings (face to face or online), agreement on diagnosis, therapeutic aims and plans for treatment and review".[115]

NICE guideline NG193 on chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain defined a PMP as "any intervention that has two or more components including a physical and a psychological component delivered by trained people, with some interaction/co-ordination between the 2".[100]

Published research evidence use a range of definitions for PMPs, for example a Cochrane systematic review of multidisciplinary biopsychosocial rehabilitation for chronic low back pain included multidisciplinary rehabilitation interventions if they "involved a physical component and one or both of a psychological component or a social/work targeted component. Furthermore, the different components had to be delivered by clinicians with different professional backgrounds, but no specific professional backgrounds were required".[113]

After reviewing the existing definitions and considering the most important requirements for PMPs in the Scottish context, the GDG agreed on the following definition of a PMP. Literature searches and recommendations in this guideline are based on these criteria.

A PMP involves interventions which are:

- psychologically informed (eg has components such as cognitive behavioural therapy (CBT) and/or pain neuroscience education (PNE)).
- comprised of multiple interventions delivered concurrently (eg exercise or physical activity, CBT, PNE, medication review).
- delivered in a group setting, either face-to-face or remotely (eg online).
- typically run over several sessions or weeks.
- led by healthcare professionals from more than one professional group (eg allied health professional, doctor, psychologist).

The systematic literature review to identify evidence for PMPs identified 2,800 potential evidence sources. Screening titles and abstracts reduced this to 25. After full-text screening, 24 were excluded: 21 did not meet the SIGN GDG definition of a PMP, and three were excluded after comparison with the 2021 review from the US Agency for Healthcare Research and

Quality (AHRQ).[116] Randomised controlled trials from the excluded three reviews were mostly included in the prioritised review, which drew similar conclusions and added no further useful evidence for PMPs.

6.3 Evidence of benefit

One high-quality systematic review with meta-analysis was selected to provide evidence on the effectiveness of PMPs.[116] This review included 57 RCTs (of low to moderate quality) that compared PMPs with a variety of alternatives (usual care, wait list or attention control, physical therapy, psychological therapy and combinations of these). Eight studies examined IPMPs (based in primary care) and 49 studies examined CPMPs (not based in primary care). Concerns about bias were low. 1++

Some of the included RCTs investigated IPMPs delivered both in group and individual settings. There was limited evidence investigating different programme factors and their impact on outcomes. Given this inconsistency, that many IPMPs do not meet the British Pain Society's definition of a PMP and that services providing IPMPs do not exist in Scotland currently, it was decided to limit the analysis to CPMPs only.

While evidence for a wide variety of musculoskeletal pain conditions is considered (chronic low back pain, chronic neck pain, osteoarthritis of the knee, hip, or hand and fibromyalgia), and musculoskeletal pain is one of the most common pain symptoms, other pain conditions are not represented within this evidence base.

6.3.1 Comprehensive Pain Management Programmes compared with usual care

Overall, CPMPs resulted in a small improvement in pain post-intervention (MD -0.53 on a 0 to 10 scale, 95% CI -0.80 to -0.25; 11 RCTs, 764 participants; moderate strength of evidence). At short- (1 to <6 months), intermediate- (≥6 to <12 months) and long-term (≥12 months) follow up, the difference was below the threshold for small effects, was not statistically significant, or both.[116]

CPMPs resulted in moderate improvements in function compared with usual care or waitlist at post-intervention follow-up (SMD -0.52, 95% CI -0.88 to -0.16; 13 RCTs, 981 participants) and short-term follow up (SMD -0.62, 95% CI -1.02 to -0.24; 7 RCTs, 1,097 participants). Heterogeneity was high with I^2 values over 80% and the strength of evidence was assessed as low. There was no evidence of a difference at intermediate and long-term follow-up timepoints. 1++

CPMPs resulted in a small effect on depression compared with usual care at short-term follow up (SMD -0.48, 95% CI -0.89 to -0.08; 5 RCTs, 543 participants). A statistically significant effect was not reported post intervention, nor sustained at intermediate- or long-term follow up.

Based on two trials, there was no evidence of an effect of CPMPs on health-related quality of life as assessed by SF-36 physical component summary (PCS) or mental component summary (MCS) scores.

6.3.2 Comprehensive Pain Management Programmes compared with physical

	activity	
	There was no significant difference in pain intensity between CPMPs and physical activity at any time point.[116]	
	A small improvement in short-term function was identified in those participants receiving CPMP (SMD -0.37 95% CI -0.61 to -0.16; 3 RCTs, 459 participants). There was no evidence of benefit post intervention or at intermediate- or long-term follow up.	1++
	There were no statistically significant differences in the severity of depression between CPMPs and physical activity post intervention, at intermediate- or long-term follow-up timepoints.	
	There were no statistically significant differences in health status between CPMPs and physical activity measured by the SF-12 or SF-36 PCS and MCS at post intervention and long-term follow-up timepoints.	
6.3.3	Comprehensive Pain Management Programmes compared with pharmacological therapies	
	There was moderate improvement in pain scores for CPMPs compared with pharmacological therapy post intervention (pooled MD -1.28, 95% CI -2.14 to -0.63; 2 RCTs, 204 participants), and a small improvement at intermediate-term follow up (pooled MD -0.84, 95% CI -1.64 to -0.15; 2 RCTs, 265 participants). Strength of evidence was low. There was no difference seen at short- and long-term follow up.[116]	
	While there was no effect of CPMPs on function compared with pharmacological therapy post intervention, small improvements were reported at short-term (SMD -0.37, 95% CI -0.67 to -0.08; 2 RCTs, 342 participants), intermediate-term (SMD -0.44, 95% CI -0.67 to -0.22; 3 RCTs, 453 participants) and long-term (SMD -0.46, 95% CI -0.76 to -0.16; 2 RCTs, 301 participants) timepoints. Strength of evidence was low to moderate.	1++
	Evidence on the impact of CPMPs on health status and measures of psychological wellbeing compared with pharmacologic therapy alone are limited. Studies using different assessment measures report conflicting findings.	
6.3.4	Comprehensive Pain Management Programmes compared with psychological therapies	
	There were no statistically significant differences between CPMPs and psychological therapies found for pain, function, health-related quality of life or depression at any timepoint.[116]	1++
6.3.5	Comprehensive Pain Management Programmes compared with combined pharmacological and physical therapies	
	There was conflicting evidence for an effect on pain from two RCTs on CPMPs compared with combined pharmacological and physical therapies. In one fair-quality RCT involving people with fibromyalgia, CPMP was associated with moderate improvements in Multidimensional Pain Inventory (MPI) pain intensity (differences -1.2 to -2.1 on a 0 to 6 scale)	

and MPI pain interference (differences -1.9 to -2.5 on 0 to 6 scale) at post intervention, intermediate-, and long-term timepoints. Only antidepressants were prescribed in this trial. In contrast, the poor-quality trial in patients with low back pain reported no difference in pain between groups post intervention (difference 0.93, 95% CI -0.19 to 2.1, on a 0 to 10 scale). Medications in this trial included diclofenac, paracetamol, and omeprazole.

There were no statistically significant differences in function between CPMPs and combined pharmacological and physical therapies reported in either of two RCTs. 1++

There was conflicting evidence for an effect on depression from two RCTs on CPMPs compared with combined pharmacological and physical therapies. Small improvements in MPI affective distress (0 to 6 scale) favouring CPMP were seen post intervention, intermediate term, and long term (differences -1.9 to -2.3) in one trial. In contrast, no difference in emotional distress based on the Profile of Mood States Short Version (POMS-SV) was seen in the other trial post intervention.

6.4 Evidence of harms

There were limited reports of adverse events for CPMPs (3 RCTs reported increased pain due to the intervention, and 1 RCT reported an adverse event due to the intervention without further details). Reporting adverse events is inconsistent and lacks detail across the evidence.[116] 1++

Since CPMPs encourage participants to carry out any movements or activities within a range that is safe and sustainable for them, harms directly related to participation would not be anticipated.

6.5 Summary of benefits and harms of pain management programmes

While the clinical significance in many of the reported outcomes is uncertain (*see section 1.4.1*), the GDG noted that results demonstrated that CPMPs were either significantly more effective or as effective as most comparators. The GDG also noted the low levels of harms reported and were aware that the published evidence may not capture all key benefits of PMPs due to reliance on measures of pain and function, rather than self efficacy and agency. The GDG also noted that the reported effect sizes of benefit were small and mostly limited to people with musculoskeletal pain conditions which limits generalisability and lowers confidence in the strength of recommendation. The guideline development group concluded that there was enough benefit from CPMPs to justify a conditional recommendation in their favour.

There remains a lack of qualitative outcomes examined in this review, nor of acceptability, cost analysis or how suitable CPMPs are for most people with chronic pain in Scotland. The GDG acknowledged that the evidence review process for this guideline was focused on analysis of systematic reviews, and that there may be surveys and focus groups presented in national meetings by PMP teams but which remain unpublished.

6.6 Other factors

Though large in landmass, Scotland's population is geographically dispersed, with 17% living in rural areas, which renders challenges to operating PMPs over such a large area.[117] The guideline development group discussed the different technologies and modes of delivery, as well as potential barriers to accessing PMPs. Innovative use of technology, as became common during the coronavirus disease 2019 (COVID-19) pandemic, is already being used by some pain services.

Qualitative outcomes were not examined and there was limited perspective from people with lived experience available. Based on their clinical experience, the GDG felt that there were other benefits associated with providing CPMPs for healthcare professionals working in pain services, such as learning as part of the multidisciplinary team and innovation and research through interdisciplinary relationships.

R **Following multidisciplinary assessment within secondary care, consider offering Comprehensive Pain Management Programmes as a treatment for people with chronic pain.**

7 Psychological interventions

7.1 Introduction

Psychological factors, alongside biological and social factors, are known to inform the experience of pain. People's beliefs, understanding and responses to living with pain may contribute to their experiences of distress and disability.[118,119]

Psychological therapies may be useful in addressing the complexity of the pain experience. The benefits of psychological therapies are described in language and concepts that are considered active in terms of response and control, in contrast to passive and catastrophising behaviours and responses. Although psychological therapies do not have big data sets of evidence, they reflect Engel's biopsychosocial model, which is the gold standard model to understand chronic pain and challenges the concept of mind-body dualism (which has the potential for stigmatisation of secondary pain experiences).[120,121]

However, the mind-body dualistic thinking remains prevalent and people who live with pain have often waited a long time to access pain services which may lead to poor confidence in or mistrust of healthcare provision.[122] Hence, it is important that the benefits of psychological therapies are presented clearly with a strong focus on being person-centred.

Evidence-based national guidelines on management of chronic pain have previously recommended acceptance and commitment therapy (ACT) and/or cognitive behavioural therapy (CBT) alongside pain management programmes, self-management programmes and mindfulness-based interventions.[100,102] Further information about delivery of psychological interventions for people with chronic pain in Scotland is available in the Matrix - a guide to delivering evidence based psychological therapies and interventions in Scotland.

4

7.2 Definitions

Cognitive behavioural therapy is an approach to engaging with how people think and behave in response to pain. CBT is founded on core principles related to addressing faulty thinking and unhelpful behaviours that result from living with pain (https://www.apa.org/ptsd-guideline/patients-and-families/cognitive-behavioral).

Acceptance and commitment therapy is a form of psychotherapy that encourages people to accept their thoughts and feelings related living with pain, to identify what they cannot control and put their energy into positive actions that enrich their lives. Outcomes targeted by ACT clinicians tend to focus on an increase in acceptance and in engagement with valued activities, rather than disability or distress. (https://dictionary.apa.org/acceptance-and-commitment-therapy).

Mindfulness-based stress reduction (MBSR) is a group intervention that seeks to reframe a person's relationship to pain through detached self-

observation. It relies on training in mindfulness meditation to cope with stress, illness and pain.[123]

Biofeedback is a form of operant conditioning where people learn how to modify some of their behavioural responses to improve their health. (https://dictionary.apa.org/biofeedback)

Relaxation is a non-pharmacological treatment which is increasingly accepted as an intervention for managing pain. The use of relaxation techniques may promote feelings of wellbeing and calmness. (https://dictionary.apa.org/relaxation-therapy)

7.3 Evidence of benefit

7.3.1 Cognitive behavioural therapy

A Cochrane systematic review with meta-analysis investigated the effectiveness of CBT and ACT delivered face-to-face for people with chronic pain.[124] The most frequently included pain conditions were fibromyalgia (19 studies), chronic lower back pain (16 studies), mixed chronic pain conditions (15 studies), rheumatoid arthritis (9 studies), osteoarthritis (5 studies) and temporomandibular disorder (4 studies). CBT was compared with either treatment as usual (TAU) which included participants being placed on a waiting list or an active control. Active comparators included exercise programmes, medical procedures, education or support group.

When compared with treatment as usual, CBT resulted in a small benefit in pain intensity (SMD -0.22, 95% CI -0.33 to -0.10; 29 trials, 2,572 participants), disability (SMD -0.32, 95% CI -0.45 to -0.19; 28 trials, 2,524 participants) and distress (SMD -0.34, 95% CI -0.44 to -0.24; 27 trials, 2,559 participants) at the end of treatment. The certainty of the evidence was moderate for pain and distress and low for disability.[124] 1++

When compared with an active comparator CBT resulted in very small benefits in pain (SMD -0.09, 95% CI -0.17 to -0.01; 23 trials, 3,235 participants), disability (SMD -0.12, 95% CI -0.20 to -0.04; 19 trials, 2,543 participants) and distress (SMD -0.09, 95% CI -0.18 to -0.00; 24 trials, 3,297 participants) at the end of treatment for people with chronic pain. Benefits were statistically significant but owing to the range of measurement scales used it was not possible to assess clinical significance. The certainty of the evidence was moderate. Benefits to pain and disability at end of treatment did not persist when outcomes at follow up of 6 months or more were considered. There was moderate certainty evidence of a small reduction in distress at follow up (SMD -0.13, 95% CI -0.25 to -0.01; 16 trials, 1,757 participants).[124]

A further Cochrane systematic review with meta-analysis examined the effectiveness of remote psychological therapies for people with chronic pain.[125] The majority of studies were in people with chronic back pain, fibromyalgia or mixed chronic pain populations. Interventions were scalable to a large group of people with chronic pain, delivered primarily through technology (such as web-based and smartphone apps and virtual

	reality) and involved less than 30% contact time with a clinician. Remote CBT resulted in small benefits in pain intensity (SMD -0.28, 95% CI -0.39 to -0.16; 20 trials, 3,206 participants, moderate certainty evidence) and functional disability (SMD -0.38, 95% CI -0.53 to -0.22; 14 trials, 2,672 participants, low certainty evidence) compared with TAU at the end of treatment. There was very low certainty evidence of no benefit on quality of life. The benefits on pain intensity did not persist at follow up of three to 12 months. There were no statistically significant benefits on functional disability or quality of life at follow up.[125] Remote CBT resulted in a small reduction in pain intensity (SMD -0.28, 95% CI -0.52 to -0.04; 3 trials, 261 participants, moderate certainty evidence) compared with active control. There was no evidence of benefit for functional disability or quality of life. Based on very low certainty evidence there was no difference between interventions at follow up.[125]	1++
7.3.2	Acceptance and commitment therapy	
	When compared with treatment as usual ACT resulted in a large benefit on pain intensity at the end of treatment (SMD -0.83, 95% CI -1.57 to -0.09; 2 trials, 162 participants). The certainty of evidence was very low. No evidence was reported regarding the outcome of disability or distress. One small study (104 participants) assessed as being very low certainty reported that ACT produced a large benefit in reducing pain intensity at six months follow up, (MD -1.10, 95% CI -1.51 to -0.69).[124] When compared with active comparators at the end of treatment there was no evidence of benefit on pain intensity (SMD -0.25, 95% CI -0.63 to 0.12; 5 trials, 385 participants) or distress (SMD -0.30, 95% CI -0.70 to 0.10; 5 trials, 385 participants). The certainty of the evidence was very low. At follow up, the finding was similar for pain intensity and for distress but for disability there was very low certainty evidence of a large benefit (SMD -1.22, 95% CI -2.28 to -0.17; 2 trials, 156 participants).[124]	1++
	For remote ACT compared with TAU there was no evidence of benefit on outcomes of pain intensity (four trials) or functional disability (two trials). In both cases evidence was assessed as very low certainty. Findings were similar for follow up at three to 12 months.[125] For remote ACT compared with active comparator therapies only one study was identified providing very low certainty evidence of likely no benefit on pain intensity at the end of treatment. Based on two trials there was very low certainty evidence of likely no benefit on quality of life at end of treatment. At follow up only one small trial (50 participants) was identified which provided low certainty evidence of no benefit on quality of life.[125]	1++
7.3.3	Mindfulness based stress reduction	
	A network meta-analysis compared CBT with MBSR for the outcomes of pain intensity, physical functioning and depression in adults with chronic pain. The review identified 21 studies, which mostly involved participants with fibromyalgia and chronic low back pain.[126] Nine trials were rated as	

poor quality.

Only one study in the network directly compared CBT with MBSR for pain intensity. Thirteen studies compared CBT with control and five studies compared MBSR with control. When the direct and indirect evidence (1,364 participants) was combined there was no evidence of a difference between the therapies (SMD 0.02, 95% Credible Interval (CrI) -0.43 to 0.48).

Only one study in the network directly compared CBT with MBSR for function. Eleven studies compared CBT with control and five studies compared MBSR with control. When the direct and indirect evidence (1,320 participants) was combined there was no evidence of a difference between the therapies (SMD -0.02, 95% CrI -0.49 to 0.42).

Only one study in the network directly compared CBT with MBSR for depressive symptoms. Nine studies compared CBT with control and six studies compared MBSR with control. When the direct and indirect evidence (1,306 participants) was combined there was no evidence of a difference between the therapies (SMD -0.06, 95% CrI -1.08 to 0.47).

In one large systematic review and meta-analysis of non-pharmacological treatments for chronic pain, there was no evidence of benefit at short term on pain from MBSR compared with usual care or attention control (where the control group completes some activities but they are not the same in intensity, time and/or contacts as the intervention activities; activities may or may not be similar to usual care) (MD -0.88, 95% CI -1.82 to 0.08; 5 studies, 630 participants, moderate certainty evidence).[127] When two poor-quality trials were excluded from the analysis there was a small statistically significant improvement in short-term pain (MD -0.68, 95% CI -1.29 to -0.28; 3 studies, 546 participants, moderate certainty evidence). One study provided evidence of improved pain at intermediate term (MD -0.75, 95% CI -1.16 to -0.34; 229 participants, low certainty evidence). 1++

For short-term function there was low certainty evidence that MBSR had no clear effect (SMD -0.14, 95% CI -0.51 to 0.02; 4 trials, 581 participants) when compared with usual care or attention control. Individual trials found no evidence of benefit for MBSR on intermediate or long-term function.

7.3.4 Biofeedback

The systematic review of non-pharmacological treatments for chronic pain identified insufficient and inconsistent evidence for biofeedback in people with fibromyalgia. Four small, poor-quality trials were identified.[127] Due to the wide range of function scales used, no meta-analysis could be conducted. Three of these studies reported no difference in function between people receiving biofeedback or attention control. The fourth trial (40 participants) compared biofeedback with escitalopram and reported improved mean Fibromyalgia Impact Questionnaire scores at 4-5 months follow up and a statistically significant improvement in pain score of -2.7 on a visual analogue scale. 1++

7.3.5 Relaxation

The systematic review of non-pharmacological treatments for chronic pain identified one poor-quality study on progressive relaxation therapy compared with usual care which showed no evidence of benefit on pain or function in people with chronic lower back pain. A further fair-quality trial found no difference in pain (0-10 scale) or function (0-80 scale) in the short or intermediate term between relaxation training and no intervention or exercise for people with chronic neck pain.[127] 1++

7.4 Evidence of harms

7.4.1 Cognitive behavioural therapy

Cochrane reviews report that adverse event data for psychological therapies in chronic pain were only recorded in a few studies and were not collected in a consistent manner. Minor events such as temporary pain exacerbation were noted. In one study of remote CBT there was an increase in adverse events, including increased pain, in the intervention group (RR 6.00, 95% CI 2.2 to 16.40; 140 participants, very low certainty evidence).[124,125] 1++

7.4.2 Acceptance and commitment therapy

Two studies reported that there were no adverse effects linked to ACT compared with active controls.[124] 1++

7.4.3 Mindfulness based stress reduction

In the systematic review comparing MBSR with usual care or attention control one trial reported temporarily increased pain in 29% of people undergoing MBSR, and three trials reported no harms.[127] 1++

7.4.4 Biofeedback

No evidence of harm was reported.

7.4.5 Relaxation

No evidence of harm was reported.

7.4 Summary of benefits and harms of psychological interventions for chronic pain

CBT, delivered either in-person or remotely, can yield small improvements in pain intensity in the short term which are not sustained over time. In-person CBT can also improve functional disability in the short term. ACT delivered in person may reduce pain compared with usual care but is no more effective than active comparators.

MSBR may have similar short-term effects on pain and function to CBT. There is no evidence of benefit of biofeedback or relaxation interventions.

The GDG noted that few harms of psychological therapies were reported, and felt most interventions to be low risk, although there is a lack of clarity on what constitutes an adverse event for psychological therapies, which may persist long term. They felt that although not the target of treatment, psychological interventions may also support individuals' mental health

and were aware that many people with chronic pain are affected by mood disorder comorbidities.

7.5 Other factors

Studies included in the cited systematic reviews used a wide range of controls or TAU conditions, such as waitlists, standard care, active treatments and attention controls, which makes drawing conclusions difficult.

None of the systematic reviews or included trials reported on the inclusion or involvement of people with lived experience. Hence there is limited information available to judge the perspectives or preferences of people living with chronic pain.

Management of chronic pain involves multidisciplinary healthcare teams which can include psychology, nursing, physiotherapy, occupational therapy, pharmacy, medical and administrative staff.[128] For the face-to-face interventions, all studies reported delivery of the intervention by a psychologist or trainee psychologist under supervision of a psychologist. The GDG discussed that in NHSScotland healthcare professionals from other disciplines may deliver some psychological interventions in line with the competency-based approach described in the Matrix. The GDG wished to reinforce the workforce competencies and skills framework, which categorises CBT and ACT within the specialist / enhanced types of psychological practices. Depending on local arrangements, further appropriate training may be required before delivering the interventions.

R **Offer CBT** (either face-to-face or remotely) **to adults experiencing chronic pain.**

R **Consider offering face-to-face ACT to manage chronic pain in people where there is a preference for an acceptance approach to pain.**

✓ CBT and ACT should be delivered either by a psychologist or trainee psychologist under supervision of a psychologist.

R **Consider offering MBSR** (regardless of delivery mode) **to manage chronic pain in people where there is a preference for mindfulness approaches to pain.**

8 Self-help interventions

8.1 Introduction

Self-management is seen as a cornerstone of chronic pain care.[100] Within the NHS, these skills are often imparted by physiotherapists in outpatient settings and by multidisciplinary pain management programs in secondary care. These programs typically involve a multidisciplinary team of pain consultants, specialist nurses, occupational therapists, pharmacists, physiotherapists, and psychologists.

Barriers exist to people's engagement with secondary care pain management programs.[129] Logistical challenges, including transportation difficulties, reliance on public transport, the costs associated with private vehicle use and parking, the navigation of hospital grounds, poor mental health or dependence on family or friends may pose hurdles.[130]

The resources in specialised pain management healthcare services within the NHS may pose another challenge. Consequently, waiting times for pain management programs are often protracted.[131] These limitations suggest a need for innovative solutions to improve the accessibility and effectiveness of pain management support for individuals living with chronic pain.

The guideline development group sought evidence on a range of interventions which involve no or minimal ongoing healthcare professional input and which are self-led, with or without intermittent supportive contact (see Annex 1). Evidence was only identified on peer support and digital self-management interventions.

8.2 Peer support interventions

Peer support has been defined as "the giving of assistance and encouragement by an individual considered 'equal' as part of a created network or intervention by 'peers' who are trained to deliver the intervention.[132]

In the context of chronic pain, the evidence base for peer support is weak, making it challenging to draw definitive conclusions about its benefits and harms.

8.2.1 Evidence of benefit

One systematic review with meta-analysis was identified which examined the effectiveness of peer support interventions for adults with chronic musculoskeletal pain.[132] Twenty-four RCTs were included, all of which were rated at high or unclear risk of bias leading to all outcomes having low or very low certainty of evidence.

When compared with usual care (9 trials) there was no evidence of benefit of peer support on pain intensity at short term (up to three months) but at medium (four to nine months) and long term (longer than nine months) peer support resulted in small reductions in pain intensity. At medium term

the scale of this was in the range of 0.35 to 6.61 points on a 100-point scale. There was no evidence of effect for peer support on pain intensity compared with waitlist control (8 trials) or active control (7 trials) at any follow-up timepoint.

When compared with usual care (9 trials) there was no evidence of benefit of peer support on function in the short or medium term. In the long term peer support was superior to usual care; SMD -0.10 (95% CI -0.19 to 0.00; 5 trials, 1,730 participants). When this measure was back-converted to the function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) the degree of benefit (2.06 points) did not reach the minimal clinically important difference of 9 points on a 0 to 68 scale (*see section 1.4.1*). There was no evidence of effect for peer support on function compared with waitlist control (6 trials) or active control (3-4 trials) at any follow up timepoint. 1++

Four studies compared peer support with usual care and found no significant effect on quality of life at any time point. Only one study compared peer support with waitlist for quality of life. While there were significant improvements in quality of life at six weeks, these were not sustained at six months. Two studies compared the effect of peer support on quality of life with active control. One reported significant improvement in quality of life whilst the other found no significant effects.

8.2.2 Evidence of harm

The systematic review did not report outcome data on adverse effects. The guideline development group noted the potential for harm in people who may be managing chronic pain themselves attributing misinformation or providing unhelpful advice. They also discussed that delivery of peer support interventions may place a burden on individuals which could represent a harm over time, and suggested that providers should establish support mechanisms to avoid this.

8.2.3 Other factors

Peer support may offer a rewarding experience for both the individuals providing and receiving support, according to qualitative and non-randomised evidence supplied by Pain Concern and Pain Association Scotland and their representatives. Self efficacy (how able you feel you are to manage your condition), depression, anxiety and specific task-related outcomes were felt to be more relevant outcomes to this intervention than pain intensity and function.

Testimony from people with chronic pain on peer support interventions includes:

- *This pain course has helped and given me such hope in such subtle ways. Amazed, such a big improvement in helping me to manage my pain better on a day-to-day basis.* (Person with lived experience after attending a Pain Association Scotland self-management course)
- *Proof you're not alone* (Feedback following sessions led by Pain Concern).

8.2.4 Summary of benefits and harms for peer support interventions

Evidence in people with chronic musculoskeletal pain showed that peer support interventions may provide a small benefit on pain intensity in the medium and long term and on function in the long term compared with usual care. No evidence was identified on people with other pain types, such as neuropathic or visceral pain which may have distinct underlying mechanisms and treatment responses, which limits the generalisability of these findings. The guideline development group noted that there may be additional benefits of peer support interventions that have not been captured in this evidence. For example, both peer supporters and recipients may experience benefits such as increased self efficacy, a sense of agency, reassurance, access to information, and improved self-management skills.

No evidence was identified on adverse effects of these interventions, however the guideline development group discussed the burden of care on peer supporters. There is a risk that peer supporters, who may themselves be managing the condition, could inadvertently offer unhelpful advice or misinformation in unsupervised settings while struggling with their own challenges.

R **Peer support interventions should be considered as part of the holistic and individualised management for people with chronic musculoskeletal pain.**

✓ Services providing peer support pain management interventions should establish mechanisms for monitoring and supporting individuals delivering peer support.

8.3 Self-management interventions

There is no ‘gold standard’ definition of self management, but it may be broadly interpreted as the day-to-day tasks an individual may undertake to control or reduce the impact of a disease on physical or psychological health status. Self management describes the individual’s ability to manage symptoms, treatment, physical and psychological consequences and lifestyle changes associated with a chronic condition.[133] While the guideline development group sought information on a wide range of self-management approaches (see Annex 1), evidence was only identified on digital self-management tools.

Three systematic reviews, all published in 2023, were identified.[134-136] Intervention definitions varied across the reviews as did the populations of interest. The three reviews encompassed a total of 48 trials. Two trials were common to all three reviews. There was inconsistency across the reviews as to the quality ratings assigned to the trials reflecting the subjective nature of critical appraisal and the different tools used.

8.3.1 Evidence of benefit

One systematic review examined the effectiveness of digital self-care

interventions for pain and function in people with spine musculoskeletal disorders (neck pain, back pain or low back pain).[134] In meta-analysis of ten out of 20 RCTs of people with chronic back pain, there was a small but statistically significant benefit of digital self-care interventions on pain intensity post-treatment; SMD -0.19 (95% CI -0.28 to -0.09; 9 trials, 1,775 participants) and small-to-moderate benefits on pain intensity at medium term; SMD -0.21 (95% CI -0.33 to -0.08; 5 trials, 940 participants) and at long term; SMD -0.24 (95% CI -0.37 to -0.11; 4 trials, 908 participants) compared with usual care. For functional disability there were small benefits of the digital self-care interventions post-treatment SMD -0.18 (95% CI -0.26 to -0.10; 9 trials, 2,513 participants) and at medium term; SMD -0.13 (95% CI -0.24 to -0.02; 4 trials, 1,207 participants) and long term SMD -0.14 (95% CI -0.25 to -0.04; 4 trials, 1,452 participants). Meta-analysis of the three RCTs of neck pain was not undertaken due to high heterogeneity (I^2=89%). Of these, two studies had positive and statistically significant findings for pain and function (clinical significance not stated) and one reported no evidence of benefit on pain.	1++
A second systematic review explored the effectiveness of mobile health (mHealth) interventions on pain, function and quality of life for people with a range of chronic pain conditions.[135] mHealth interventions were diverse and apps included combinations of the following components: • monitoring and tracking of physical activity and healthy lifestyle goals • symptom monitoring • treatment delivery (such as physical activity programmes, cognitive behavioural therapy and pain education). Meta-analysis was not undertaken due to the heterogeneity across the study interventions and outcome measures, therefore results were presented narratively in terms of statistically significant benefit or no difference per RCT. The most frequent pain conditions were osteoarthritis, lower back pain and neck pain. Intervention duration ranged from 4 to 24 weeks and follow up from none (measures at end of intervention) to six months. Separately, for pain intensity and for functional disability, ten of the 17 studies assessing each outcome reported statistically significant effects for mHealth interventions compared with controls. Two and one of these studies, respectively, were at high risk of bias. The extent and clinical significance of the benefits was not assessed. Six of 15 studies which assessed quality of life found benefits for mHealth interventions. One of these was at high risk of bias.	1+
A third systematic review with meta-analysis examined the effect of digital self-management interventions (either using a digital intervention accessible via smartphone/smartwatch/tablet/computer or internet browser, or using a guided or unguided self-management technique) on various aspects of pain (intensity, catastrophising and	1++

interference/disability) for people with chronic low back pain.[136]

In meta-analysis of 12 RCTs there was a small improvement in pain intensity post-treatment as a result of the digital self-management intervention (SMD 0.24, 95% CI 0.09 to 0.40; 12 trials, 1,545 participants). Pain interference (which encompassed pain disability) showed a small-to-moderate improvement as a result of the intervention (SMD 0.43, 95% CI 0.27 to 0.59; 11 trials, 930 participants). There was no statistically significant benefit on pain catastrophising. When all three pain concepts were combined into one measure there was a small-to-moderate positive effect of the intervention (SMD 0.33, 95% CI 0.17 to 0.49; not stated). Sensitivity analysis identified that this positive effect was lost when only studies at low risk of bias were included (SMD 0.08, 95% CI -0.18 to 0.34; not stated).

8.3.2 Evidence of harm

The systematic reviews noted that most included trials did not present adverse event data, and one review did not evaluate harms.[136] Where events were reported, they were mainly related to increase in pain associated with increased physical activity.

8.3.3 Other factors

The widespread adoption of digital interventions may exacerbate existing health inequalities. Individuals with limited digital literacy, access to technology, or reliable internet connectivity may be excluded from these services, potentially widening the gap in healthcare access. Furthermore, the profit-driven nature of commercial interventions' development raises ethical concerns regarding the prioritisation of financial gain over optimal patient outcomes. The guideline development group also noted that it was not always clear how digital tools maintained the security of individual's data and expressed concern about data privacy.

The GDG noted that NHSScotland digital facilitators deliver an important role in transforming healthcare for those who lack access to technology. Facilitators:

- deliver support to clinical staff and service users to build their confidence and ability to join virtual programmes and interventions.
- work with library service colleagues to support those without devices or connectivity. There are some loan schemes in operation.
- work with organisations who deliver digital interventions to help them reach those who lack access to technology.

The feasibility of delivering digital self-management interventions as a prescribed treatment option has not been evaluated. While they may potentially reduce the need for certain healthcare resources, the initial costs of funding access to individuals and supporting their use must be considered.

Given the wide range of digital interventions reviewed, assessing their specific feasibility and economic impact in real-world Scottish settings is complex. Further research is needed to identify practical barriers and

facilitators to implementation, as well as to evaluate the cost effectiveness of these interventions.

8.3.4 Summary of benefits and harms of self-management interventions for chronic pain

Digital self-management interventions have a small effect on reducing pain intensity and functional disability with little evidence of harms. As these interventions most commonly involve exercise and physical activity, education and CBT, potential benefits and harms are likely to be associated with the facilitation of these interventions (see section 7).

The effectiveness of digital interventions may vary across different chronic pain conditions. While promising results have been observed in musculoskeletal pain, further research is needed to evaluate their efficacy in other chronic pain conditions, such as neuropathic pain or fibromyalgia and to clarify optimal delivery pathways.

R **Digital self-management interventions should be considered as part of the holistic and individual management of chronic musculoskeletal pain.**

✓ As digital self-management tools can, in themselves, be a barrier to practising self care for people who do not have access to, or are not able to use, digital tools, hybrid models of care, whereby they receive support from a digital facilitator or healthcare professional that encourages them to self care, should be available.

Data security measures should be clearly explained to people in an easy-to-understand way, fostering trust and transparency. When recommending digital support interventions for chronic pain management, it is crucial to prioritise safety and trust in people with lived experience.

✓ Robust measures must be in place to ensure the confidentiality and security of all patient data.

9 Occupation-based interventions

9.1 Introduction

What constitutes a meaningful activity will vary from person to person, and might include hobbies, exercise, social activities or employment (paid and voluntary). Chronic pain can hinder people engaging in meaningful activities, affecting their self-care, productivity and/or leisure occupations. Occupation-based interventions in the context of chronic pain support individuals to engage in meaningful activities even in the presence of pain. Occupation is defined by the World Federation of Occupational Therapists as 'the everyday activities that people do as individuals, in families and with communities to occupy time and bring meaning and purpose to life'.

Reducing pain intensity is not an intended outcome of occupation-based interventions, although some may report changes in their pain experience. These interventions help individuals identify valued activities and align well with the ACT model of psychological flexibility. Engagement in meaningful activities can support improvements in areas such as mood, motivation, independence, routine and sense of purpose. Activity management interventions, informed by pain science, can improve a person's ability to do more over time despite ongoing pain.

Occupational-based interventions are often part of wider programmes of self-management input (in a secondary care pain service, and/or a tertiary level PMP) and can be difficult to measure their impact as stand-alone interventions. They vary in delivery and tend to be person-centred, making objective comparison challenging.

9.2 Evidence of benefit

Three systematic reviews on the effectiveness of occupation-based interventions for chronic non-malignant pain were identified. These focused on pacing,[137] return to work (RTW)[138] and sleep hygiene.[139] While sleep hygiene was initially included in the search parameters, after review of this evidence, the GDG noted that it aligns more closely with sleep-focused interventions than occupation-based ones. A review of the sleep hygiene evidence base would be best carried out alongside non-pharmacological sleep interventions for people with chronic pain which falls outside of the remit of this guideline, and this systematic review was not considered further.

After excluding sleep hygiene, the evidence base consisted of 18 RCTs across two intervention areas (RTW and pacing). The evidence was inconclusive due to variations in study design, RTW and pacing definitions, and intervention delivery formats, making it difficult to support any specific RTW or pacing approach for people with chronic pain. In addition, occupational performance and participation in meaningful activities were not an outcome focus for these trials.

A systematic review of 13 RCTs examined the effectiveness of RTW | 1+

interventions from sick leave for people with chronic pain.[138] The primary outcome was RTW which was measured in a range of ways including number of days per month without receipt of sickness benefit, self-reported return to occupation, early retirement rates and cessation of wage loss. Most of the studies involved multiple components and there was a wide range of control conditions. Duration of intervention and follow up also varied and heterogeneity across the studies meant that meta-analysis was not possible.

Five of the 13 studies showed statistically significant improvements in RTW however three of these five studies were assessed at being at high risk of bias.

A narrative systematic review of 5 RCTs examined the effectiveness of pacing as a learned strategy for people with chronic pain.[137] Meta-analysis was not possible due to heterogeneity in interventions and outcome measures. Based on three studies which reported pain outcomes, the review concluded that pacing as a learned strategy does not significantly reduce pain in people with chronic pain due to osteoarthritis or fibromyalgia. The GDG note that this finding is in line with expectations as the aim of this intervention is improved function rather than pain reduction and none of the interventions used an occupation-based approach in which pacing was implemented practically within an occupation under the guidance of a therapist. 1+

An additional literature search at RCT level identified no studies on other occupation-based interventions, including energy conservation strategies, postural and positional strategies, sensory integration strategies, therapeutic education and disease self-management training, advocacy skills development, community reintegration strategies, environmental adaptations/equipment provision, and engagement in meaningful daily activity/meaningful occupation.

9.3 Evidence of harms

There are limited reports of adverse events in the occupation-based intervention evidence base. One RTW trial focusing on CBT resulted in delayed RTW versus usual care. Findings highlight a need to consider RTW intervention effectiveness and potential hinderance or delay of RTW.[138] 1+

Since occupation-based interventions encourage people to engage in self-identified movement and activities in a way that is within their capacity, it would not be anticipated for harm to be directly related to these interventions.

9.4 Other factors

The GDG discussed issues relating to the design and implementation of research studies in the field of RTW and pacing interventions. They acknowledged that focusing RTW interventions purely on the primary outcome of return to work is reductive and risks excluding other important benefits. They considered that returning to the same work doing the same hours may not necessarily be the 'good' outcome for an individual, and noted that acceptance, considering values and quality of life or returning to meaningful activities (such as caring for grandchildren or helping at a community club) can lead to people enacting changes in their work and personal lives. Linking people with employability services can aid career changes and training needs. Confidence and satisfaction in work roles can be more accurate indicators of occupational outcomes.

A UK government website acknowledges the link between employment and health and states ‘there is clear evidence that good work improves health and wellbeing across people’s lives, not only from an economic standpoint but also in terms of quality of life’. It defines good work as ‘having not only a work environment that is safe, but also having a sense of security, autonomy, good line management and communication within an organisation.’ Conversely a difficult work environment and unsupportive management can lead to increased stress and pressure and be unhelpful to an individual's pain management.

The GDG discussed that pacing interventions delivered from a symptom reduction compensatory approach can lead to functional decline and increased activity avoidance. When pacing interventions are delivered in such a way and interpreted as being limited to taking breaks, slowing down activities and spacing out tasks this alone does not encompass the many facets involved in the activity management occupation-based intervention. This may lead to clinicians unintentionally supporting activity restrictions and limitations that may then reduce function rather than improve function. There is value in occupation-based interventions being delivered by clinicians with knowledge of facilitating conversations around planning, grading, chunking, alternating and monitoring activity underpinned by acceptance, awareness psychologically informed methods.

9.5 Summary of benefits and harms of occupation-based interventions for chronic pain

The low volume of evidence with inconsistent findings is insufficient to support recommendations. Variations in study designs, heterogeneity across studies, and differences in RTW and pacing definitions impact on generalisation to the wider chronic pain population. Even in the context of low volume evidence, expert clinicians acknowledge that work and activity dysregulation issues are common amongst the chronic pain population and to not address these issues would mean disregarding needs identified by people with lived experience.

The evidence base shows little to no evidence of harm related to

occupation-based interventions. Expert clinicians highlight areas for consideration for measuring RTW interventions and for the delivery of pacing (activity management) interventions.

✓ Clinicians should be aware that activity management (pacing) interventions focused on symptom reduction may inadvertently lead to greater activity avoidance. However, activity management interventions which are underpinned by a values-based approach, pain science education, and delivered by psychologically-informed clinicians may encourage greater activity engagement, improving both occupational performance and satisfaction.

✓ The term “pacing” is too narrow to fully capture the scope of activity management interventions. Clinicians are encouraged to move away from exclusively using the label “pacing” and instead adopt terms like “activity management” or “activity regulation”. These terms better encompass the many facets involved in the intervention.

✓ Clinicians and people living with chronic pain should understand that occupation-based interventions are not intended to reduce pain. Instead, these interventions aim to increase occupational performance and satisfaction, participation in life roles, participation in social functioning, and engagement in personally meaningful occupations within the domains of self-care, productivity and leisure

✓ Clinicians delivering work-related occupational interventions to individuals with chronic pain should adopt a holistic approach, considering both performance and satisfaction in relation to employment and wider life roles. The intervention may include, but not be limited to addressing:

- quality of life,
- satisfaction with work life balance,
- confidence and ability to communicate needs in the workplace,
- support in negotiating reasonable adjustments,
- the ability to regulate during and outside working hours,
- confidence to manage flare-ups and work absences, and
- balancing life roles alongside work and chronic pain management.

10 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

10.1 Implementation strategy

Implementation of national clinical guidelines is the responsibility of each NHS board, including health and social care partnerships, and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Quality improvement methodologies can be used locally to implement the guidelines. The Quality Improvement Journey contains generic advice and tools to use quality improvement methods to support local implementation. NHS Education for Scotland also delivers the Scottish Improvement Leaders programme and Scottish Quality and Safety Fellowship programme to develop individuals to lead local implementation projects to improve the quality of care.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

10.2 Resource implications of key recommendations

No recommendations are considered likely to reach the £5 million threshold which warrants resource impact analysis.

10.3 Auditing current practice

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

CONTENT IN DEVELOPMENT

10.4 Health technology assessment advice for NHSScotland

In August 2006, the Scottish Medicines Consortium (SMC) advised that duloxetine (Cymbalta®) is accepted for restricted use for the treatment of diabetic peripheral neuropathic pain in adults. It is restricted to initiation by prescribers experienced in the management of diabetic peripheral neuropathic pain as second- or third-line therapy.

https://scottishmedicines.org.uk/media/1590/duloxetine__cymbalta_285_06.pdf

11 The evidence base

11.1 Systematic literature review

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a Healthcare Improvement Scotland Information Scientist. Databases searched include Medline, Embase, PsycINFO and the Cochrane Library. The year range covered was 2018–2024. Internet searches were carried out on various websites for relevant guidelines. The main searches were supplemented by material identified by individual members of the development group. Critical appraisal of relevant evidence was carried out by Healthcare Improvement Scotland Health Service Researchers or NHS Research Scotland (NRS) Pain external researchers. Each of the selected papers was evaluated by two researchers using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

The search strategies will be available on the SIGN website, www.sign.ac.uk when this guideline is published.

11.1.1 Literature search for lived-experience issues

At the start of the guideline development process, a Healthcare Improvement Scotland Information Scientist conducted a literature search for qualitative and quantitative studies that addressed issues on the management of chronic pain relevant to people with lived experience of chronic pain. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Advisor and presented to the guideline development group. Group members were also made aware of a report published by the Health and Social Care Alliance Scotland (the ALLIANCE). As the national third sector intermediary for health and social care, in 2021 the Scottish Government asked the ALLIANCE to conduct a survey that would be used to inform their ongoing work on chronic pain policy. Based on responses gathered from 462 people, the report describes how chronic pain impacts their day-to-day life, the level of importance placed on public information about chronic pain and how to access support.[140] Key points are summarised in section 1.1.1

11.2 Recommendations for research

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (see Annex 1). The following areas for further research have been identified:

Opioids

- Studies to quantify the risk of adverse events, including overdose and substance use disorder in people being prescribed opioids for pain management, and to develop accurate risk predication

instruments. These should include assessment of risks associated with co-prescribed medications.

- Studies of comparisons of benefits and harms experienced according to different personal and pain characteristics, and different types of opioid.
- Studies to determine effective risk mitigation strategies in people who are prescribed opioids.
- Studies to identify the efficacy and adverse events of long-term (>12 month) opioid use.
- Studies to identify optimal opioid tapering/de-prescribing strategies, type of support and services, that also assess the benefits and harms associated with de-prescribing.

Naloxone

- Studies to assess the impact of naloxone prescribing on the incidence of fatal and non-fatal overdose events in people prescribed opioids for chronic pain, with a particular focus on other factors that may increase an individual's risk of overdose (eg comorbidity, polypharmacy, demographics).
- Studies to evaluate the acceptability of naloxone use, including the willingness of this population and their families, and how this may change management of their chronic pain and use of opioids.

Antidepressants

- The safety and efficacy of antidepressants used for longer than three months in the treatment of chronic pain
- The safety and efficacy of antidepressants in people with chronic pain comparing effects between those with and without a diagnosis of clinical depression

Medicinal cannabis

- High quality RCTs with appropriate duration of follow up are needed to identify clinically relevant harms and benefits of medicinal cannabis in the treatment of chronic pain, with outcome measures aligned to IMMPACT recommendations. Where standard RCT designs may be inappropriate to adequately address the question(s) other robust trial designs should be considered.
- Studies to assess effects in specific populations, eg neuropathic pain; older adults; multimorbidity; polypharmacy.
- Longer term studies are needed to identify harms that may take time to develop such as dependence and mental health issues.
- Studies to assess potential interactions between different formulations of medicinal cannabis and medications commonly-used by people living with chronic pain.

Pain management programmes

- Studies to investigate how best to capture behavioural change following participation on a PMP. (In practice PMPs are designed to promote behavioural change in the service of improving quality of life in the presence of persistent pain. Changes that individuals report following completion of a PMP are often not reflected in changes in the outcome measures used to quantify effects in the historical research evidence. We know that individual items on the outcome measures we use can mean different things to people living with chronic pain and clinicians. The use of irrelevant outcome measures makes it harder to properly evaluate the role of PMPs).
- Studies are required to assess long-term clinical and cost effectiveness of PMPs measured in terms of effects on mood, anxiety, quality of life, medication usage, activity levels, fear of movement, disability, pain intensity, psychological flexibility and measures of primary and secondary healthcare utilisation, in addition to qualitative descriptions of change in activity, wellbeing and behaviour.
- The GDG is aware of individual UK PMPs having presented outcome data at national meetings but this valuable data is then not submitted or does not reach publication. We propose a collaborative research network of PMP providers within the UK. This pooled, multicentre and international approach may lead to better data for a wider variety of outcomes. A national audit is proposed using the audit points which will be suggested with this guideline.
- Further information is required on qualitative outcomes associated with PMPs. Published evidence commonly doesn't reflect lived experience of change and there is a need for greater incorporation of the perspective of people living with chronic pain, including local viewpoints which take into account cultural and societal differences.
- Further information is required on factors that affect the suitability of people for CPMPs, and how to target a population who are likely to benefit, and systematically comparing individual vs group-based PMPs to better understand how different modes of delivery, intervention components and dose characteristics influence outcomes and subjective experiences.

Psychological interventions

- In order to establish the generalisability of interventions, further high-quality RCTs are needed which include adults with a wide variety of chronic pain conditions.
- Further studies are needed that include long-term follow-up periods of all outcomes (including acceptance and cost-effectiveness, where appropriate)
- In general, studies of psychological interventions should establish

greater standardisation of control conditions

- In general, further studies are needed using appropriate outcome measures that match the goals of the intervention (for example, daily functioning). More specifically, further studies are needed which assess acceptance and valued activity as outcome measures, as these better align with ACT focus.
- Further studies are needed to establish adverse events using clearer, consistent definitions and standardised reporting on adverse events (including long-term adverse events)
- Further studies are required that compare intervention delivery modes directly with each other (ie, face-to-face versus remote delivery, and delivery by psychologists versus non-psychologists)

Self-help interventions

- Research is needed to improve the understanding of the acceptability, engagement, and adherence in digital support interventions.
- Studies are needed to quantify the impact of peer support on both peer supporters and recipients, including emotional wellbeing, social connectedness, and quality of life, for both groups.
- Studies should examine the qualities and skills that contribute to successful peer support, such as empathy, active listening, and problem-solving abilities.
- Research should focus on designing and implementing effective training programs to equip peer supporters with the necessary knowledge and skills.
- Long-term follow-up studies are needed to assess the sustainability of the effects of peer support interventions and to measure any potential long-term benefits or harms.

Occupation-based interventions

- Further studies are required to establish the effectiveness of the wide range of occupation-based interventions.
- Further high-quality studies are required to establish the effectiveness of RTW interventions. Researchers should consider defining a core outcome set and/or comparative outcomes to be used in trials to enable comparability across multiple studies.
- Further studies in people with chronic pain who are unemployed and want to return to work, and people who are struggling to manage their pain condition while in work could help widen the literature base for subgroups where literature lacks.
- Further studies are required to capture the impact of RTW interventions on the person’s satisfaction with their work-life balance and confidence to manage their pain condition in the workplace.

- Researchers should consider investigating activity pacing among populations with other types of chronic pain conditions beyond osteoarthritis or fibromyalgia to improve the generalisability of evidence. Also, to use valid and reliable outcome measures and justification of sample size to improve qualities of studies.
- Further studies of activity pacing for people with chronic pain are needed to investigate different intervention conditions such as length and frequency of intervention sessions. Also incorporating an occupation-based therapy approach.
- Additional research is indicated to investigate the effectiveness of pacing as a learned strategy in the activity and participation outcome domains in determining the impact that pacing can have on a person's ability to participate in daily occupational and life roles.

12 Development of the guideline

12.1 Introduction

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at **www.sign.ac.uk**

This guideline was developed according to the 2019 edition of SIGN 50 with the following adaptations. In their first meeting, the guideline development group agreed a set of key questions for review which was later packaged into smaller work programmes of 4-6 questions each, known as waves. Each wave proceeded with dedicated systematic literature searching, screening and selection, critical appraisal and evidence synthesis. For each wave, the guideline development group developed draft recommendations and guideline text which will be consulted on separately. This document contains information relating to waves one and two. The guideline development group will incorporate revisions based on feedback received at consultation and from editorial reviewers and the final version of each wave will be published online as a toolkit within the Right Decision Service, the 'Once for Scotland' source of digital tools that enable people to make safe decisions quickly, based on validated evidence. Although published individually over a period of time, the full set of digital materials for all waves assembled on the Right Decision Service will collectively represent the SIGN guideline on chronic pain.

12.2 The Guideline Development Group

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The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available on request from the SIGN Executive.

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Guideline development and literature review expertise, support and facilitation were provided by SIGN Executive and Healthcare Improvement Scotland staff. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on request from the SIGN Executive.

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SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

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Ms Carrie Stewart	Research Fellow, University of Aberdeen

12.3 Consultation and peer review

A report of the consultation and peer review comments and responses will be published in the supporting material section for this guideline on the SIGN website. All expert referees and other contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

12.3.1 Specialist reviewers invited to comment on this draft

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12.3.2 Public consultation

The draft guideline was also available on the SIGN website for a month to allow all interested parties to comment.

12.3.3 SIGN editorial group

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on request from the SIGN Executive.

Dr Roberta James	*SIGN Programme Lead; Co-Editor*
Professor Angela Timoney	*Chair of SIGN; Co-Editor*
Dr Safia Qureshi	*Diector of Evidence, Healthcare Improvement Scotland*

Abbreviations

ACT	acceptance and commitment therapy
AHRQ	Agency for Healthcare Research and Quality
BNF	British National Formulary
CBD	cannabidiol
CBT	cognitive behavioural therapy
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPMP	comprehensive pain management programme
CrI	credible interval
D&OUD	dependence and opioid use disorder
ED	emergency department
GDG	guideline development group
GDP	gross domestic product
GMC	General Medical Council
GP	general practitioner
HR	hazard ratio
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
IPMP	integrated pain management programme
IR	immediate-release
IRR	incidence rate ratio
LOCF	last observation carried forward
MA	marketing authorisation
MBSR	Mindfulness-based stress reduction
MCID	minimum clinically-important difference
MCS	mental component summary
MD	mean difference
MED	morphine-equivalent dose
mHealth	mobile health

MOR	mu opioid receptor
MPI	Multidimensional Pain Inventory
MR	modified-release
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NNTH	number needed to harm
NRS	NHS Research Scotland
NSAID	non-steroidal anti-inflammatory drug
ODI	Oswestry Disability Index
OR	odds ratio
OUD	opioid use disorder
PCS	physical component summary
PGIC	Patient Global Impression of Change
PMP	pain management programme
POMS-SV	Profile of Mood States Short Version
PNE	pain neuroscience education
PNS	peripheral nervous system
QoL	quality of life
RCT	randomised controlled trial
RDQ	Roland-Morris Disability Questionnaire
RR	relative risk or risk ratio
RTW	return to work
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SMD	standardised mean difference
SmPc	summary of product characteristics
SPACE	Strategies for Prescribing Analgesics Comparative Effectiveness trial
SUCRA	surface under the cumulative ranking curve
TAU	treatment as usual
TCA	tricyclic antidepressant
THC	tetrahydrocannabinol
USA	United States of America
VAS	visual analog scale

WHO	World Health Organization
WMD	weighted mean difference
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Annex 1
Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Guideline section	Key question	
2	1.	In people with chronic non-malignant pain are opioids more likely than placebo or other interventions to improve pain severity, functional ability, and/or quality of life, and/or to cause adverse events/drug reactions, or dependency (physiological or psychological)?
3	2.	Should naloxone be coprescribed when opioids are used for chronic pain (or when long-term/high-dose opioids are prescribed)?
4	3.	In patients with chronic non-malignant pain what is the effectiveness of medicinal cannabis compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse drug reactions or dependency (physiological or psychological)?
5	4.	In patients with chronic non-malignant pain what is the effectiveness of antidepressants compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions or dependency (physiological or psychological)?
6	5.	In patients with chronic non-malignant pain, what is the effectiveness of pain management programmes (as defined in the guideline) compared with no treatment or other interventions on pain scores, functional ability, mood, quality of life and adverse events?
7	6.	In patients with chronic non-malignant pain what is the effectiveness of psychological interventions (cognitive behavioural therapy, acceptance and commitment therapy, mindfulness-based interventions, biofeedback or relaxation) compared with no treatment or other interventions on pain scores (30% reduction and 50% reduction), functional ability, mood, quality of life or adverse events?
8	7.	In patients with non-malignant chronic pain what is the effectiveness of patient and lay self-help advice compared with no treatment or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life or

		adverse events? Interventions were considered which had no or minimal ongoing healthcare professional input (which can potentially reach large numbers of patients) and which are generally self-led, with or without intermittent supportive contact, including • apps (mobile and web-based/mhealth, ehealth), • computer-based programmes • monitoring devices eg exercise trackers • automated reminders/ brief telephone support to follow programme or take actions • bibliotherapy/advice booklets/manuals • lay self-help or support groups, eg third-sector groups • mentoring/support by peers.
9	8.	In patients with chronic non-malignant pain what is the effectiveness of occupation-based interventions on pain scores (30% reduction and 50% reduction), occupational performance, engagement in personally meaningful occupations, return to work rates, quality of life or adverse events?

Information relating to the following questions will be made available in future consultations

Not included in this draft	9.	In patients with chronic non-malignant pain what is the effectiveness of muscle relaxants compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse drug reactions or dependency (physiological or psychological)?
Not included in this draft	10.	In patients with chronic non-malignant pain what is the effectiveness of simple analgesics compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions or dependency (physiological or psychological)?
Not included in this draft	11.	In patients with chronic non-malignant pain what is the effectiveness of topical analgesics compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions or dependency (physiological or psychological)?
Not included in this draft	12.	In patients with chronic non-malignant pain what is the effectiveness of anti-epilepsy drugs compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse drug reactions or dependency (physiological or psychological)?
Not included	13.	In patients with chronic non-malignant pain what is the effectiveness of combination pharmacological therapies

in this draft		compared with single pharmacological therapies on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions or dependency (physiological or psychological)?
Not included in this draft	14.	In patients with chronic non-malignant pain what is the effectiveness of hands-on based interventions (manual therapies or massage) compared with comparator on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events?
Not included in this draft	15.	In patients with chronic non-malignant pain what is the effectiveness of hands-off based interventions (exercise, physical activity or mobility aids) compared with comparator (see table) on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events?
Not included in this draft	16.	In patients with chronic non-malignant pain what is the effectiveness of electrotherapy-based interventions (TENS, interferential, laser therapy, pulsed-shortwave diathermy, ultrasound, microcurrent therapy, or shockwave therapy) compared with comparator on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events?
Not included in this draft	17.	In patients with chronic non-malignant pain what is the effectiveness of other/alternative interventions (acupuncture, aromatherapy, homeopathy, herbal medicine, hypnotherapy, music therapy or Reiki) compared with comparator on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events?
Not included in this draft	18.	In patients with chronic non-malignant pain is there any evidence for the effectiveness of dietary interventions compared with usual care on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events?

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